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Department of Health and Human Services

Health Care Financing Administration

Report to Congress

"Lung Volume Reduction Surgery and Medicare Coverage Policy: Implications of Recently Published Evidence"

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SUMMARY

In the Department of Health and Human Services Appropriations Act, 1997, Congress required the Health Care Financing Administration (HCFA), with the advice and technical assistance of the Agency for Health Care Policy and Research (AHCPR), to report to Congress on the treatment of end-stage emphysema and chronic obstructive pulmonary disease and on unilateral and bilateral lung volume reduction surgery (LVRS) and supplemental surgical methods. HCFA was asked to review all available studies and, based on this review, make a recommendation as to the appropriateness and conditions of Medicare coverage of such procedures. This report responds to that requirement

LVRS encompasses procedures intended to improve lung function for emphysema patients and relieve debilitating symptoms of the disease. LVRS diffused rapidly from 1993-1996, despite a paucity of medical evidence concerning its safety and efficacy. Moreover, there are considerable debates within the medical community not only about the appropriateness of surgical intervention, but also concerning the relative merits of a variety of surgical approaches, appropriate selection of patients, and the contribution of comprehensive pulmonary rehabilitation

In December 1995, HCFA issued a noncoverage policy for all LVRS procedures based on the lack of medical evidence and potential for extensive morbidity and mortality among Medicare beneficiaries. HCFA also requested the Center for Health Care Technology (CHCT), which is part of AHCPR, to undertake a complete review of available evidence, published or unpublished. Over the same period of time, the National Heart, Lung and Blood Institute (NHLBI) also became interested in the medical issues concerning LVRS. A September 1995 workshop sponsored by NHLBI called for controlled studies. In April, 1996, the CHCT report was released Based on an analysis of approximately 2800 patients from 27 institutions, the report

concluded that the available data did not permit a scientific conclusion regarding the risks and benefits of LVRS. The report recommended that since some patients appeared to benefit in the short run, Medicare coverage might be provided within a controlled clinical study. Later that month, HCFA and NHLBI signed an agreement to participate in such a study. As part of this agreement, NHLBI would design and fund the study and HCFA would provide reimbursement for the medical care services provided to Medicare's beneficiaries treated under the study's protocol. The study is now known as the National Emphysema Treatment Trial (NETT).

The NETT represents a precedent setting cooperative effort between the nation's largest payer and its premier science agency for research on pulmonary diseases and may serve as a model for future assessments of important new technologies. Medicare beneficiaries will be provided controlled access to a promising but in many ways unproven procedure, while scientifically valid data to guide future use and reimbursement decisions are generated.

As is true for many new technologies in the U.S. health care system, many parties are interested in its rapid diffusion. Emphysema affects millions of individuals with substantial disability, morbidity and mortality. LVRS offers hope of improved quality of life for some of these patients. Because of the potentially large number of patients that might be eligible for this surgery, there is also a considerable financial interest in LVRS on the part of providers and manufacturers. Therefore, it is understandable that there would be interest in broader Medicare coverage of LVRS than is provided under the NETT. This report provides detailed explanations of the study, an assessment of recent data concerning LVRS and details of how modifications to Medicare coverage policy will be made.

The NETT

The NETT is a multi-center clinical trial designed to determine the efficacy of two surgical

approaches to bilateral lung volume reduction median sternotomy and video assisted thoracoscopy surgery (VATS) This study will compare the efficacy of maximal medical therapy and one of these procedures versus the efficacy of maximal medical therapy alone Efficacy will

be determined with regard to a variety of patient outcomes including lung function measures, exercise tolerance, medical care service use, a variety of quality of life measures and mortality. Eighteen clinical study centers, including 21 hospitals are now participating in the study.

The final study protocol has been developed by the Steering Committee (SC) for the NETT, comprised of the principal investigators and investigators from the clinical centers and the study's coordinating center. Enrollment of patients in the study began in November 1997. The study also includes a Data Safety Monitoring Board (DSMB) which reviews the study data quarterly If at any time the DSMB finds the data conclusive -- that is, one of the study treatments is providing clear benefit or harm -- they will recommend either the study be terminated or the protocol be modified

Under the clinical protocol for the NETT, patients will be randomly assigned to median sternotomy with maximal medical therapy, VATS with maximal medical therapy, or maximal medical therapy alone Maximal medical therapy includes state of the art medical care and intensive pulmonary rehabilitation The randomized design was initially chosen by NHLBI and ratified by the EC for the final protocol for two reasons First, because there is no existing data on the natural history for this group of patients, many of the most critical questions about the risks and benefits of LVRS can only be answered within a randomized design Second, current data do not allow for a conclusion regarding the relative risks and benefits of LVRS or the contribution to outcomes of maximal medical therapy Therefore, there should be no pre-disposal as to the preferred course of treatment In this report, we review the most recent evidence with regard to these reasons

The NETT protocol does not include unilateral or laser approaches to LVRS. From existing data, it appears that bilateral excision approaches to the surgery have a greater potential to be efficacious than unilateral or laser techniques. For this reason, consensus within the medical community now favors the bilateral excision approaches as the primary modalities. It is possible that the other approaches may have selected roles such as unilateral for patients unable to tolerate bilateral surgery; and laser as an adjunct to excision. Once the effectiveness of the bilateral approaches has been established, coverage of the other procedures can be considered for these circumstances.

Future Medicare Coverage Decisions Regarding LVRS

LVRS is now covered only when provided under the clinical study protocol of the NETT. However, HCFA is committed to modifying this policy rapidly in response to new and scientifically conclusive data regarding LVRS. The explicit contingencies for modification of Medicare coverage are part of the agreement between HCFA and NHLBI.

First, current coverage is conditioned on the study protocol and changes automatically in response to study design and analysis of evidence. The protocol now expects approximately 4,700 patients to be recruited for the study within the next four and one half years. Unless the data demonstrate harmful effects, Medicare coverage will be continued after these recruitment goals have been met in a manner consistent with the emerging evidence or need for further evidence. More importantly, even before recruitment goals have been met, Medicare coverage will be modified promptly to reflect any finding of conclusive evidence by the DSMB, NHLBI, or HCFA. For example, if the DSMB were to recommend and NHLBI agree that some group of patients were achieving a clear benefit from LVRS, coverage would be expanded. Depending on the evidence, such expansions might take place in the study centers, or new criteria established for its provision

in hospitals outside of the study. Likewise, a finding of clear ineffectiveness or harm for some patients would trigger a noncoverage policy targeted to that group.

What do Recently Published Data Suggest About the Appropriate Course of Action for Medicare?

We reviewed 26 recently published articles regarding LVRS for this report. A set of evidence-based criteria for systematic review was applied, including examination of study design, outcomes measured and patient follow-up. In addition, we examined Medicare databases in order to provide supplemental information on patients' morbidity and mortality following surgery.

The conclusion from this review is essentially the same as that of the AHCPR/CHCT assessment and an assessment for the American Lung Association. While some patients appear to benefit for a short period of time in terms of selected measures of lung function, dyspnea measures and exercise capacity, the most critical questions concerning the risks and benefits of LVRS for particular patients cannot be adequately answered by existing data. Indeed, the data review heightened the importance of producing scientifically valid evidence concerning the durability of any benefits and mortality during a reasonable post-surgical period. Thus, the most appropriate course for Medicare on behalf of its beneficiaries remains the scientific path reflected in the NETT. That is, the data suggest enough potential for benefit that some Medicare coverage should be provided, but only under the conditions that increase the likelihood that the service can be delivered safely to beneficiaries and that will generate the medical evidence needed to answer critical questions about the value of this surgery.

These conclusions result from several inherent weaknesses in the published data concerning LVRS. First, the published articles present case series data rather than evidence from carefully structured and controlled clinical studies. While the authors involved should be commended for

reporting outcomes data, case series are generally considered as a weak and potentially misleading form of evidence concerning the effect of therapeutic interventions. Moreover, while an important test for the value of LVRS will be its risks and benefits over a reasonable time period -- e.g. 1-2 years -- most available studies report patient experience at 3-6 months. In addition, the majority of studies measure what are considered surrogates for the patient outcomes of interest. Thus, the impact of LVRS on quality of life, use of medical care services and mortality is yet to be determined.

One of the most substantial problems with available studies is the high percentage of treated patients that could not be followed in the post-surgical period in order to assess their outcomes. This problem is particularly true for data beyond 3 months post-surgery and may result in considerable bias for reported outcomes. The most comprehensive study examined outcomes at 6 and 12 months. Two-thirds of the patients had available information at 6 months after surgery and slightly more than one-third at 12 months. The study reported favorable changes in selected outcome measures at both of these times periods. To the extent that the large number of missing patients differ systematically from those that can be followed, any reported change in outcomes may be due to such selection bias rather than the actual impact of the surgery on all patients that were treated.

Finally, analysis of Medicare claims data highlights these concerns. Beginning in October 1995, a specific ICD-9 code was assigned to LVRS. We identified 722 claims for LVRS that used this code between October 1995 and January 1996. Of these patients, approximately 30% (215) had died within 18 months of their surgery -- a mortality rate considerably higher than reported or projected by the published studies. These analyses also demonstrate that the use of hospital, rehabilitation, and long term care facilities increased considerably for these patients in the year following surgery compared with the year prior to surgery. Both facts underscore that outcomes reported in the published studies may be biased -- that is more favorable than would be reflective

of all Medicare patients treated with LVRS. Moreover, because it appears that LVRS patients are at high risk with regard to morbidity and mortality in the post-surgical period, a controlled study is necessary to distinguish between the impact of the procedure on these outcomes and the impact of the disease itself.

Conclusion

We believe that the scientific, yet flexible approach to coverage of LVRS outlined in this report remains the appropriate policy course for Medicare. HCFA strives to assure access to safe and effective services for Medicare beneficiaries, while not providing reimbursement for ineffective and harmful services. Despite a number of published articles regarding LVRS, a scientific conclusion concerning the relative risks and benefits of these procedures cannot be made from existing data. By providing coverage within the clinical study, Medicare is making a precedent setting effort to provide controlled access to a promising, yet unproven procedure while assuring that the needed medical evidence is created.

INTRODUCTION

Lung Volume Reduction Surgery (LVRS) encompasses a number of procedures that are being developed to relieve the symptoms of severe emphysema. During a brief period prior to January 1996, some of these surgeries were reimbursed unknowingly by the Medicare program because they were represented as other lung procedures for purposes of billing the Program. Medicare did not have a national or any local policies that provided coverage for LVRS during that period of time. In December of 1995, the Health Care Financing Administration (HCFA) published a national noncoverage policy for these procedures. In April, 1996, after a full assessment by the Center for Health Care Technology (CHCT) which is part of the Agency for Health Care Policy and Research (AHCPR), HCFA and the National Heart, Lung, and Blood Institute (NHLBI) agreed to a long-term controlled study to determine the safety and efficacy of some LVRS procedures. The study is now known as the National Emphysema Treatment Trial (NETT). Medicare coverage of LVRS is now provided to patients treated under the protocol developed for the NETT.

The NETT represents a precedent setting effort between the nation's largest payer and its premier science agency for the study of pulmonary illnesses. The study will provide scientifically valid data for evaluating the safety and effectiveness of LVRS, and potentially guide its use to severely ill patients likely to benefit and away from those that may be harmed.

The Congress has raised some questions concerning the NETT and Medicare coverage of LVRS. These questions concern the range of procedures included in the clinical study, and on what schedule Medicare will make new coverage decisions affecting LVRS. Section 212 of the Department of Health and Human Services Appropriations Act, 1997 mandated the Health Care Financing Administration (HCFA) prepare a report to the Congress of the United States concerning LVRS. This mandate also required that HCFA obtain advice and technical assistance from the AHCPR in the development of this report. Specifically, the bill requested HCFA report to include 1) a review of available studies and research data on the treatment of end stage emphysema and chronic obstructive pulmonary disease by LVRS procedures; and 2) a recommendation as to the appropriateness of Medicare coverage for such procedures and the conditions for such coverage.

The following report describes current Medicare coverage, the NETT, the use of data that has been published since the completion of the CHCT technology assessment on this issue, and how future changes in Medicare coverage will respond to such data and the data that are generated by the clinical study. It also provides a systematic review of recent published data concerning the safety and effectiveness of LVRS as well as analysis of Medicare data regarding patients that underwent this procedure prior to the noncoverage decision.

PREVALENCE AND TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) is among the top five leading causes of death in the United States. Emphysema is one of several diseases collectively referred to as COPD. Emphysema is a chronic lung condition characterized by irreversible enlargements of airspaces in the lung, progressive loss of elastic recoil of lung tissue and airway, and the destruction of alveolar walls. As a result of these deficiencies, gas exchange is compromised and an efficient system of inhaling oxygen and exhaling carbon dioxide is impossible. Although an emphysematous lung may be somewhat easily inflated, it is difficult to expel carbon dioxide. When this occurs, the lungs become hyperinflated, which means that an excessive amount of air is trapped in the lungs. Continual hyperinflation of the lungs will cause the diaphragm to flatten and prevent the rib cage from moving up and down easily during breathing. Breathing becomes difficult and tiring. As a result, emphysematous patients suffer from chronic shortness of breath.

Various medical treatments have been used in order to treat the symptoms associated with emphysema. Since there is no cure for this form of COPD, all medical and surgical treatments, including LVRS, used for patients with emphysema are considered palliative rather than curative.

One critical step in the standard treatment of patients suffering from emphysema is smoking cessation. Because cigarette smoking has contributed to a significant number of cases of emphysema, as well as other lung and respiratory diseases, patients are encouraged to stop smoking. In addition, patients with emphysema should reduce or avoid exposure to environmental pollutants that may exacerbate this disease. Such pollutants include second-hand smoke as well as industrial by-products and waste released in the air.

Other elements in the medical therapy regimen for an emphysematous patient include annual influenza vaccinations, protein replacement therapy, drug therapy and oxygen therapy. Routine influenza vaccinations are recommended for most people, however it is critical that people with emphysema receive them in order to reduce the risk of contracting viral pneumonia. Protein replacement therapy may be beneficial for some patients with alpha1-antitrypsin deficiency. This form of therapy helps to counteract the imbalance between proteases and antiproteases in the lung that lead to the destruction of the alveolar septa. In addition, standard treatment for end-stage emphysema patients consists of pharmacologic therapy, which often includes steroids, and oxygen therapy

Although standard medical therapy may provide some relief for the emphysematous patient, it has a limited impact on quality of life and survival. Despite the various medical approaches available, the progressively destructive nature of emphysema will result in the severe deterioration of the patient's physical condition that ultimately will cause extreme debilitation. Since medical therapies for the treatment of emphysema are limited significantly, physicians throughout this century have turned to numerous surgical interventions in an attempt to provide relief to emphysema sufferers

Procedures Developed to Combat Symptoms Associated with Emphysema

In 1906, Dr. W. A. Freund proposed the theory that the thoracic cage may be too rigid to accommodate hyperinflated lungs. Through a procedure called costochondrectomy the costal cartilage and perichondrium would be resected in order to expand the size of the rib cage. The purpose of this operation was to increase the mobility of the chest wall, which would enable the lungs to expand and to contract more effectively. Although some patients reported relief of dyspnea, the overall results of costochondrectomy were unpredictable.

The next surgical approach developed to relieve the symptoms associated with emphysema was thoracoplasty. In the 1920's, Dr. H. Voelcker hypothesized that increased mobility of the hemithorax would occur if the distorted rib cages of emphysema patients were reshaped and made to resemble the downward slant of more normal chests. After performing several thoracoplasties, it was determined that changing the angle of the rib cage actually decreased vital capacity because of the increased rigidity on the side of the body that the procedure was performed.

Another procedure introduced in the 1920's was pneumoperitoneum, which was developed by Dr. L. Reich. This procedure as based on the premise that air pumped into the abdomen would elevate the diaphragm, thus improving breathing. Patients who had pneumoperitoneum experienced some relief of dyspnea and increased exercise tolerance. However, specific patient selection criteria for this procedure were not developed. In addition, patients complained of abdominal pain and were extremely inconvenienced by the biweekly refills of air that this procedure required. As a result, pneumoperitoneum was never accepted generally in the medical community.

The abdominal belt was another alternative developed to alleviate symptoms associated with emphysema. In 1934, Drs. H.L Alexander and W.B. Kountz theorized that dyspnea was caused by a shortened and immobile diaphragm. Breathing could be made easier if the diaphragm was in an elevated position. By elevating the diaphragm, the natural curvature of the organ would be restored and contraction and function could be improved. However, the abdominal belt had significant problems. Not only was the belt impractical for daily use, but it also could be used only on patients with prominent abdomens.

Another attempt at surgically treating emphysema came in 1947 when Dr. P.R. Allison decided to expand upon Dr. Voelcker's theory of thoracoplasty. Dr. Allison developed a surgical technique that was meant to increase ventilation and vital capacity by phrenic nerve paralysis. This procedure was called phrenicectomy. It was only after patients experienced worsened dyspnea that it was discovered that phrenicectomy actually reduced the motion of the ipsilateral hemithorax and diaphragm as well as the mobility of the contralateral hemithorax in cases of thoracoplasty. As a result, this procedure was quickly abandoned.

In the 1950's, several surgical alternatives were proposed for the treatment of symptoms

associated with emphysema. The first was the partial pleurectomy, which was introduced by Dr. G.L. Crenshaw. The theory behind this procedure was that the degenerative nature of emphysema could be halted if more blood could be pumped to the lungs. Partial pleurectomy, however, never gained favor in the medical community. Dr. Crenshaw later admitted that a patient who was unable to breathe efficiently would not be helped by increasing the circulation of blood to the lungs.

The second surgical intervention developed in the 1950's was lung denervation, introduced by Dr. O.A. Abbott. Lung denervation was proposed to decrease bronchospasm, reduce mucus formation and increase pulmonary circulation. Most of the denervation techniques developed that were aimed at relieving dyspnea were performed in conjunction with resection of lung tissue. Since there were numerous techniques used, the reported results were often confusing and difficult to interpret.

It was also in the 1950's that the precursor was developed for the modern procedures collectively know as lung volume reduction surgery. Drs. O.C. Brantigan, E. Mueller and M.B. Kress pioneered an innovative approach that would remove the functionless areas of the lung so that the lung could once again properly fit in the pleural space on full exhalation. It was hypothesized that volume reduction for diffuse emphysema would improve lung function by restoring the elastic recoil of small airways, improve the movement of the diaphragm and reduce the size of the rib cage. This procedure was performed via sequential bilateral thoracotomy. Although some patients reported relief of dyspnea, the significant morbidity and high operative mortality associated with volume reduction prevented this procedure from gaining wide acceptance in the medical community at the time.

It was not until decades later that Brantigan's theories were revisited and refined. Due to scientific advances in surgical techniques and the success of lung transplantion, modern surgeons have introduced new alternatives based on theories from the past in an attempt to treat emphysema. Three surgeries for emphysema that have gained significant media exposure in recent years are bilateral pneumectomy with staples via median sternotomy, unilateral or bilateral video assisted thoracic surgery with staples and unilateral thorascopic laser pneumoplasty.

Bilateral pneumectomy with staples via median sternotomy was pioneered by Dr. J.D. Cooper after his extensive experience with lung transplantation. After studying the works of Dr. Brantigan, Dr. Cooper hypothesized that the principles of volume reduction may be applied to certain patients with COPD as a alternative to or bridge to lung transplantation. The goal of this surgical approach is to remove relatively non-functional areas of the lung from emphysema patients in an attempt to relieve dyspnea and to improve exercise tolerance.

The bilateral median sternotomy technique, which is an open procedure that involves breaking the patient's breast bone, is performed on both lungs during the same operation with the most damaged lung reduced first. One lung is deflated while the other lung is ventilated. During deflation, the healthy portions of the lung collapse and the diseased portions remain inflated. The

diseased areas remain filled with air because the blood flow to these areas is poor or nonexistent. Excision of the diseased areas is performed through a stapling technique. After this process is completed, the lung is reinflated to determine if an adequate amount of lung tissue was removed. If additional lung tissue should be excised, the entire process is repeated. Surgeons are cautious to excise only small amounts of tissue at a time because significant problems are associated with post-operative air spaces in the pleural cavity when too much lung is removed. Generally, the overall volume of the lung is reduced by 20%-30%. A common post-operative complication that occurred in Dr. Cooper's early procedures was air leakage. This problem was alleviated after Dr. Cooper began using bovine pericardium strips to buttress the staple line.

Another lung volume reduction technique that has gained prominence is video-assisted thorascopic surgery (VATS), which is less invasive than the median sternotomy approach. This approach has been performed both unilaterally and bilaterally. The major difference between this procedure and the median sternotomy is the way the surgeon obtains access to the lungs. While the median sternotomy is an open chest procedure in which a vertical incision is made through the sternum, VATS is done by placing surgical instruments and a probe through smaller incisions made in the chest and pleural cavity of the patient.

The third modern lung volume reduction procedure is unilateral thorascopic laser ablation, which was introduced by Dr. A. Wakabayashi in 1989. Dr. Wakabayashi theorized that laser ablation of lung tissue would increase respiratory capacity by lessening hyperinflation. As a result, gas exchange would improve and breathing would be easier. Generally, laser ablation is performed on one lung at a time. After the patient has gone through post-operative therapy and the first lung is healed, laser ablation may be performed on the remaining lung.

Dr. Wakabayashi's approach utilizes the Nd:YAG laser probe. After the lung has been deflated, the probe is brushed over the diseased portions of the lung. The area instantly collapses and is excised by an endoscopic stapler. The surgeons who perform laser ablation of the lung are also careful about the amount of lung tissue that is removed during the procedure. This procedure must be done conservatively in order to prevent removing excessive functioning lung tissue that is found beneath the diseased area.

LVRS AND MEDICARE REIMBURSEMENT

Medicare's current coverage policy concerning LVRS appears at section 35-93 of the Coverage Issues Manual (CIM). This section states that unilateral or bilateral LVRS by open or thoracoscopic approach is not covered generally because there is insufficient medical evidence available to base a determination that this procedure is safe and effective. Therefore, LVRS cannot be considered reasonable and necessary under section 1862(a)(1)(A) of the Social Security Act in most cases. LVRS and related services are covered, however, when provided under the clinical study protocol developed for the NETT. This section describes Medicare's coverage criteria and policies, and the application of these to LVRS

Medicare's Coverage Principles

HCFA is charged with the responsibility to administer the Medicare program through Title XVIII of the Social Security Act (the Act). Arguably, the most important provision in this title of the Act is Section 1862(a)(1)(A), which is often the basis for HCFA's coverage authority. This section states that notwithstanding any other provision of this title, no payment may be made under Part A or Part B for expenses incurred for items and services which "are not reasonable and necessary (emphasis added) for the diagnosis and treatment of illness or injury or to improve the functioning of a malformed body member." "Notwithstanding any other provision of this title" means that the requirements of this section, i.e., that a service must be reasonable and necessary, override all other provisions of the Medicare statute. Even if a service is provided for in the statute, in the regulations or in one of the manuals, that service must be reasonable and necessary or else it will not be covered by Medicare.

In the more than 30 years that have passed since the implementation of the Medicare program, one of the primary responsibilities and challenges for HCFA has been to maintain a dynamic decision making process to assure that the program keeps pace with medical technology change on behalf of its beneficiaries. Although the processes and criteria for doing so have evolved as necessary to meet scientific and health care industry trends, HCFA's discretionary decisions concerning new technologies has always been guided by Section 1862(a)(1)(A) of the Act.

In order to determine whether and under which conditions a service is reasonable and necessary, and therefore covered, HCFA has developed the following criteria:

1) Demonstrated effectiveness

2) Appropriateness

3) Comparability to alternative services

Demonstrated Effectiveness

Demonstrated effectiveness means that there must be authoritative evidence that the benefits of a service outweigh the reasonably anticipated risks for its intended uses. There are two parts to this criterion. First, if the item or services is regulated by the Food and Drug Administration (FDA), it must have the relevant approval or clearance from that agency to be considered for coverage. Second, whether regulated or not, there must be sufficient scientific evidence to demonstrate that the service improves the patient outcomes deemed relevant for its intended uses.

The first part of this criterion provides a key linkage between FDA status and Medicare coverage. Because FDA approval or clearance is considered as authoritative evidence that at least some basic safety and efficacy issues have been resolved, such decisions are considered as the minimum

level of evidence required for coverage. The second part of the demonstrated effectiveness criterion, however, means that while these FDA decisions are necessary for Medicare coverage, they may not be sufficient. Because the safety and efficacy issues that must be resolved for FDA approval or clearance may or may not address key Medicare requirements concerning patient outcomes, value and relative effectiveness, FDA approvals do not guarantee Medicare coverage.

Appropriateness

To meet the criterion of appropriateness, a service must be consistent with the patient's needs and condition, provided in a setting that is commensurate with a patient's needs and by personnel who are qualified on the basis of training, experience and licensure. For example, it may be considered appropriate for some patients to undergo cardiac catheterization in a freestanding facility, but not appropriate for patients at high risk for complications related to the procedure. For the latter group, the service would only be covered in a facility with necessary support services such as a hospital.

Comparability

Comparability applies when the evidence is sufficient to allow comparison of the relevant costs and effectiveness of two or more technologies that are closely related in terms of being used for the same diagnostic or therapeutic purpose. Services that meet the demonstrated effectiveness and appropriateness criteria will be covered under conditions dictated by the evidence. Comparability is an additional criterion which allows for refining coverage/payment decisions in cases where services are found to be more costly, but no more effective than the closely related alternatives. When such a finding is made, the service may be covered and paid at the rate of the lower cost alternative, or limited to specific patients or conditions for which it has been found more effective than the alternative services. The objective of this criterion is to assure value for the Medicare program and its beneficiaries.

Evidence-Based Decisions

HCFA, like many private health insurers, has progressively adopted evidence-based procedures in order to make coverage determinations consistent with the criteria described above. While the term "evidence-based" may have different interpretations across the industry, some basic characteristics do exist:

1) A focus on patient outcomes rather than intermediate or surrogate outcomes,

2) A focus on effectiveness as opposed to efficacy; and

3) Systematic review and grading of medical evidence.

Outcomes

Several types of outcomes might be the focus of clinical studies including patient outcomes (e.g. mortality, quality of life), intermediate outcomes (changes in hematocrit, blood pressure), or surrogate outcomes (tumor shrinkage). Studies of the effectiveness or efficacy of new technologies have often focused on the latter two. However, HCFA seeks evidence of improved patient outcomes in order to make a favorable coverage determination. One reason to prefer such measures is that they represent the impact of a service on health status in ways that are more meaningful to patients (reduced pain and suffering, increased functioning). Moreover, there is a growing number of examples in which intermediate or surrogate outcomes can be poor predictors of health status change, in some cases being misleading in ways that might endanger patients (2). In evaluating services for coverage, Medicare places considerable emphasis on evidence of improvements in outcomes such as morbidity, mortality, quality of life, functional status, and changes in the use of medical care services.

Efficacy vs. Effectiveness in Clinical Studies

In examining evidence to determine the impact of a technology on patient outcomes, increasing attention is being paid to the distinction between these two commonly used terms. Efficacy can be defined as the benefit of a technology for a particular use under ideal conditions such as those that might exist under clinical study protocols. Effectiveness can be defined as the benefit of a technology when used under routine conditions found in general practice -- that is, in typical settings, practice patterns, and for patients that may differ in many ways from those in clinical trials. HCFA must carefully consider whether coverage policies must be targeted to particular facilities, patients or indications to assure that its beneficiaries can realize any beneficial effects found in clinical studies.

Systematic Review of Evidence

A universal aspect of the trend toward evidence-based processes is the systematic manner in which medical evidence is reviewed, graded, weighted and combined to guide coverage or practice decisions. These steps are intended to allow for a judgment concerning the strength of the evidence for drawing inferences about the impact of a service on patient outcomes. Formal technology assessment has evolved from a process that often examined the technical properties of a technology, to a structured review of evidence geared toward drawing conclusions about how the technology affects patient care.

In applying systematic review, HCFA prefers evidence published in peer reviewed journals. HCFA recognizes, however, that when a technology is evolving, there may be valuable evidence that is available but not yet published. Moreover, it is recognized that publication is not always a guarantee of peer review, or that data are valuable for assessment purposes. Therefore, in many cases HCFA relies on formal assessment of published and unpublished data by the AHCPR and

private assessment entities. Regardless of whether HCFA relies on an external assessment or reviews data internally, evaluation and grading of medical evidence focuses on the following key questions: were the appropriate outcomes measured; was the study design (e.g. randomized trial, case series etc.) adequate to draw inferences about these outcomes; were there a sufficient number of patients; how were patients selected; was the follow-up period of sufficient length; was follow-up complete and consistent; and can the results be generalized to Medicare patients in standard practice settings

Coverage with Conditions

Often, systematic review of medical evidence results in very difficult policy choices with regard to a particular service. Available evidence may be sufficient to resolve some basic safety and efficacy issues about a new technology and therefore, establish that the service is "promising" in terms of benefiting patients. Frequently, however, this evidence is insufficient to evaluate and draw conclusions concerning many critical questions about the risks and benefits of the service for patients -- that is, the service remains "unproven" in many regards. For example, the evidence may allow some conclusions to be drawn about the impact of the service on intermediate or surrogate outcomes, but be insufficient to evaluate its impact on morbidity, mortality and quality of life. Of equal importance, often the evidence does not allow for the development of appropriate patient selection criteria or conditions of use in standard practice.

Developing coverage policies based on such limited evidence can have several adverse consequences for the Medicare program and its beneficiaries. A noncoverage policy could slow or terminate the innovation of a potentially valuable technology due to financial pressures. On the other hand, in these cases evidence is inadequate to structure coverage policy or guide medical practice with appropriate conditions and limitations for use of the service. Thus, reimbursement might result in a diffusion of the service that is too rapid given the limited information and in ineffective or harmful care being provided to patients. Moreover, reimbursement and rapid diffusion precludes or makes very difficult the careful study of the service that would be needed to provide the needed medical evidence.

In response to these challenging policy issues, HCFA has developed innovative alternatives to the yes/no coverage decision. One such alternative is known as coverage with conditions which is designed to: 1) provide beneficiaries with controlled access to promising, yet unproven, technologies in a manner that uses the limited information available to maximize the likelihood the service can be delivered safely and effectively, and 2) help to generate data that are needed to inform and direct future coverage decisions. A key objective of coverage with conditions is to advance medical knowledge about the effectiveness of services before they diffuse to general practice and assure that Medicare beneficiaries are not at undue risk from their use. Coverage with conditions may include limitations on use, data collection, or the provision of the service under protocol conditions. These efforts may be implemented by making payments only to providers that are involved in clinical study protocols developed by NIH, FDA, other federal agencies and private research entities.

Coverage with conditions may be used when existing data suggest a potential benefit to some patients, but there is not sufficient information to predict the effect of generalized use of the technology, to evaluate important long-term outcomes or to determine appropriate patient selection criteria. Services meeting the following criteria may be considered for coverage with conditions:

> The service is of substantial interest for Medicare coverage because potentially it would affect a large number of beneficiaries or provide an important new benefit to some;
>
> Enough information exists about the service for HCFA to judge that some basic safety and efficacy issues have been resolved and therefore, the service can be considered reasonable and necessary under particular conditions;
>
> The service is unproven with regard to significant questions remaining about risks and benefits that must be answered for a final coverage decision;
>
> The information necessary for HCFA to make a national coverage decision is unlikely to be developed by researchers unless coverage with conditions is offered; and
>
> Regulated services used with the service in question are generally approved for marketing by the Food and Drug Administration.

It is HCFA's long-standing policy that, in general, services covered in clinical trials cannot be reimbursed. It is the above criteria that differentiate coverage with conditions from clinical trials that are designed to examine services for which basic safety and efficacy issues have not yet been resolved.

Medicare and LVRS

During 1995, HCFA staff began examining LVRS after being alerted to its development and potential rapid growth through several sources. The issue first came to the attention of the HCFA staff in 1995. At this time, LVRS was discussed internally as a procedure that should be assessed and considered for a national coverage decision. HCFA began a dialogue with the medical community and evaluated the existing medical evidence. After researching the clinical literature available at the time, HCFA staff was able to locate only one published article on LVRS. Thus, there was considerable concern about the dearth of scientific evidence and clinical data regarding the safety and effectiveness of this procedure and the lack of patient selection criteria. In light of the fact that the clinical evidence on LVRS was scarce, and concern in the medical community that the rapid diffusion of this procedure could result in significant risks to Medicare beneficiaries, HCFA staff made two decisions. First, a national noncoverage policy was issued. Second, HCFA officially requested a technology assessment to be performed by the CHCT within AHCPR in

order to evaluate emerging evidence on this procedu

The national noncoverage policy for LVRS was published in December 1995 as transmittal 83 in the Coverage Issues Manual (CIM). This national noncoverage policy may be found at Section 35-93 of the CIM entitled "Lung Volume Reduction Surgery (Reduction Pneumoplasty, Also Called Lung Shaving or Lung Contouring) Unilateral or Bilateral by Open or Thoracoscopic Approach for Treatment of Emphysema and Chronic Obstructive Pulmonary Disease-Not Covered."

Since HCFA issued this manual instruction without a specific effective date, the local contractors had the discretion to make the necessary systems changes in order to operationalize this policy and educate providers through bulletins within a reasonable amount of time. It is HCFA's understanding that all of the contractors were implementing the national noncoverage policy by the first quarter of 1996.

On August 30, 1995, HCFA officially requested CHCT to perform a technology assessment on LVRS. Specifically, HCFA was interested in information concerning the safety and effectiveness of this procedure by any open or percutaneous method in light of clinical trials as well as published and unpublished literature related to this service. In addition, HCFA wanted a list of medical conditions, patient selection criteria and facility selection criteria associated with LVRS.

In November 1995, CHCT issued in the Federal Register a request for information regarding LVRS. Interested parties were encouraged to submit any and all materials available on LVRS and related services. CHCT would consider published as well as unpublished scientific findings, clinical studies, articles and raw data. Those interested in providing information to CHCT had 60 days following the publication of the request to submit material. At the same time, HCFA staff also began to review a number of papers that were entering the medical literature.

On April 23, 1996 HCFA received a copy of CHCT's final technology assessment along with a signed recommendation regarding Medicare coverage. The conclusion of the report was as follows:

> "... it cannot reasonably be concluded at this time that the objective data permit a logical and a scientifically defensible conclusion regarding the risks and the benefits of LVRS as currently provided ... a prospective trial of LVRS under uniform protocol requirements with comprehensive long-term postoperative follow up data is both ethically supportable and scientifically essential."

The report stated that there was no consensus within the thoracic surgery community regarding which LVRS technique delivered the most favorable results or if specific indications correlate with particular approaches. The community was also at odds over the issue of bilateral LVRS in comparison to unilateral LVRS. Second, variable outcomes such as pulmonary function tests, oxygen dependence, quality of life measures and exercise tolerance revealed a lack of

comprehensive and uniform patient selection criteria, surgical procedures and pulmonary rehabilitation programs among facilities performing LVRS.

Most importantly, the CHCT report found several weaknesses in the existing data concerning LVRS that made drawing a conclusion about the procedure's safety and effectiveness difficult. These included a lack of follow-up data and insufficient documentation of benefits resulting from the procedure. According to the assessment, operative and perioperative mortality ranged from 5% to 10%. In addition, the long term benefits associated with LVRS, such as patient functional status and survival were unknown.

It should be noted that the assessment did maintain that an unknown percentage of patients with severe COPD did well after LVRS. However, there remain a number of crucial unanswered questions regarding this procedure. For instance, more information regarding which procedure is the most safe and effective, well-defined patient-selection criteria, the characteristics integral to a facility furnishing LVRS and the role and function of pulmonary rehabilitation. Ultimately, CHCT recommended that HCFA consider a "prospective trial of LVRS under uniform protocol requirements with comprehensive long-term postoperative follow-up data." The AHCPR recommendation, in conjunction with HCFA's examination of the emerging literature and contact with concerned providers, resulted in the conclusion that LVRS fit all the criteria for coverage with conditions (1).

LVRS Coding Issues

In addition to examining emerging literature and consultations with the medical community throughout this period, HCFA also began data analysis from the Medicare claims system. A temporary billing code was established for LVRS (G0061) in January 1996 until the permanent CPT code became effective January 1, 1997. Since there were no specific procedure codes assigned to LVRS prior to the temporary code that was effective January 1996, it is unknown precisely how many of these procedures were performed on Medicare patients. In order to receive payment from Medicare for LVRS, some providers were using codes assigned to other types of lung surgery that were paid for by the program. These covered services include bullectomy, wedge resection and lobectomy.

The implications of not having specific codes for LVRS prior to January 1996 were two-fold. First, Medicare never knowingly paid for LVRS because some providers were using codes for covered lung procedures rather than miscellaneous codes when filing claims for LVRS. Therefore, when the noncoverage policy was established, many incorrectly assumed that Medicare had discontinued coverage of LVRS. Since there was never a national or local policy for LVRS prior to the noncoverage policy issued in December 1995, HCFA did not withdraw coverage

Second, the lack of a specific procedure code for much of the period prior to 1996 makes some data analyses difficult in terms of differentiating LVRS from other lung procedures. In October of 1995, an ICD-9 procedure code was assigned for LVRS. Therefore, some analysis is provided

later in this report using procedures billed with this code during the last quarter of 1995.

HCFA/NATIONAL HEART, LUNG AND BLOOD INSTITUTES'S NATIONAL EMPHYSEMA TREATMENT TRIAL (NETT)

As with any new procedure that holds promise to treat severely ill patients, there is a considerable interest in seeing LVRS made available as soon as possible. Unfortunately, the desire and ability to innovate and rapidly diffuse these technologies often exceeds the scientific evidence that is needed to make clinically appropriate decisions on how to use them. In particular, many procedures find their way to widespread use before the relevant benefits and harms can be assessed and the proper patient selection criteria developed. The medical literature documents a growing number of medical services that have entered general medical practice based on incomplete evidence and have later been shown to be ineffective or harmful (2).

Nonetheless, the issues associated with medical evidence and its relationship to reimbursement are complex. Several groups have raised concerns about how soon expanded Medicare coverage may be forthcoming, how the study data will be linked to new coverage for the procedures studied, and how further consideration will be given to procedures not included in the clinical study such as unilateral LVRS and laser procedures. In addition, misunderstandings about the study design have lead some concerned groups to significantly underestimate the potential number of patients treated during the study and reimbursed by Medicare. In this section, a detailed discussion of all of these important issues is provided.

Background

Following publication of the national policy in the CIM, HCFA began a dialogue with the NHLBI, which is within NIH. Independently, NHLBI was focusing on issues related to LVRS at the same time HCFA was making national coverage policy decisions on this procedure. In the winter of 1996, HCFA and NHLBI held several discussions concerning the potential for cooperative efforts related to assessing LVRS. One strategy discussed was a randomized, multi center clinical study to the extent that design was supported by an assessment of the most recent data. That support was provided by the CHCT assessment and recommendation.

On April 24, 1996 a joint press release was issued stating that HCFA and NHLBI would collaborate on a clinical study regarding LVRS. The purpose of this multi-centered randomized study, which includes a prospective registry examining the role of LVRS, is to evaluate the long-term outcomes of the procedure on function, morbidity and mortality as well as to define appropriate patient selection criteria.

After extensive communication and negotiations between HCFA and NHLBI, a Memorandum of Understanding (MOU) was signed by both agencies in June 1996. This MOU describes the purpose of the clinical study, the authority provided to each agency enabling participation in the

study, the background issues associated with COPD and LVRS, the scope of work and responsibilities for HCFA and NHLBI as well as administrative details that make this cooperative effort a valid government project.

NHLBI is responsible for negotiating, awarding and administering all contracts related to the study and providing some administrative costs. In addition, NHLBI must monitor program performance, which includes making decisions based on information received from the Data and Safety Monitoring Board regarding issues such as patient safety and early termination of the trial.

HCFA is responsible for providing reimbursement to the participating clinical facilities for patient care costs related to services received as part of the study. During the randomization phase, HCFA will provide reimbursement for those services furnished to Medicare beneficiaries participating in the respective clinical arms of the study. After the randomization goals of the study have been met, HCFA will issue revised coverage policies based on the scientific conclusions that can be drawn from the study data. These contingencies are discussed in greater detail in a later section of this report. Additional responsibilities for HCFA during the study include review of all proposals, attending Steering Committee meetings and providing technical reports and program data integral to the study.

On May 9 and 10, 1996, NHLBI announced the study in the Commerce Business Daily. This is the usual forum NIH uses to announce projects. The announcement informed interested parties that a Request for Proposals (RFP) would be available on or about June 3, 1996 via the NIH RFP Gopher for facilities and clinical coordinating centers who would like to apply for participation in the study. Originally, the deadline for facilities to submit their proposals was August 5, 1996, however that deadline was extended to August 19, 1996.

In September 1996, NHLBI convened a panel of experts in cardiothoracic surgery, statistics of clinical outcomes research and pulmonology to review the proposals of the clinical facilities. A second group of experts in statistics and scientific analysis were responsible for reviewing the proposals of the clinical coordinating center. On December 20, 1996, HCFA and NHLBI issued a press release announcing that contracts were awarded to 18 facilities who will perform LVRS and furnish related services to those patients randomized in the study. In addition, one contract was awarded to a clinical coordinating center

Important Features of the NETT with Regard to Medicare Coverage

The objective of the NETT is to establish a seven-year multi-center randomized clinical trial in association with a prospective registry to evaluate the long-term efficacy, morbidity and mortality associated with intensive medical therapy with LVRS as compared to intensive medical therapy alone, and to define patient selection criteria. The actual treatment phase of the trial is expected to last four years beginning late December 1997. A secondary objective of the study protocol is to define which patients benefit from the procedures. LVRS will be performed bilaterally either by median sternotomy or VATS with lung surgical excision (stapling). The primary end points of

the study are improved exercise capacity and survival. Secondary end points will be morbidity, improvement in pulmonary function, quality of life and performance of activities of daily living.

It is expected that NETT will determine: 1) the potential role of LVRS in the treatment of emphysema patients; 2) the efficacy of LVRS compared to intensive medical and rehabilitative therapy in improving function as assessed by success with activities of daily living, improvements in quality of life, dyspnea scores, pulmonary function, morbidity and mortality; 3) patient selection criteria for LVRS, and 4) the efficacy of LVRS by median sternotomy versus VATS.

NETT will follow and analyze two groups of patients; those in the registry and those in the randomized trial. The registry will include patients who have undergone diagnostic testing for NETT at any of the 18 participating clinical centers. Patients in the registry who meet selection criteria will be invited for inclusion in the randomized study. Patients in the registry will be followed from data in the National Death Index and HCFA data bases. The registry will provide information on patients referred for LVRS, will provide data on the outcomes of these patients, will provide a source of patients for randomization and will allow comparison of patients who are randomized to the larger pool of patients with end-stage emphysema, both to determine the validity of applying results and to verify that the randomized groups are representative.

The NETT protocol requires the recruitment of 4700 patients over the 4.5 year period beginning with November 1997. Patients meeting eligibility requirements will be randomized to receive either maximal medical therapy in combination with LVRS or only maximal medical therapy. LVRS will be performed bilaterally either by median sternotomy or VATS. Thus, three types of comparisons will be made: 1) medical therapy alone versus medical therapy with LVRS by median sternotomy, 2) medical therapy alone versus medical therapy with LVRS by VATS, or 3) medical therapy alone versus medical therapy with LVRS by median sternotomy versus medical therapy with LVRS by VATS. Maximal medical therapy will include pulmonary rehabilitation and education. Direct comparisons of the two surgical techniques will be possible only at the centers that are performing both techniques.

An important feature of the NETT for determining its operations is the Executive Committee. The Executive Committee is composed of the chairman of the Steering Committee (SC), representatives from the coordinating center and NHLBI, and the three chairmen of the protocol workgroups for Phase I of the contract. The voting membership of the NETT SC includes the principal investigators and co-principal investigators from each clinical center, the principal investigator from the coordinating center, the NHLBI project officer, and Chairman of the NETT Steering Committee. Other governmental components, such as HCFA and AHCPR, are invited to attend the SC meetings, however they are precluded from voting when motions are presented.

The charge of the NETT SC is to design the study's protocol, manual of operations and all reporting and data forms. This includes developing patient consent forms and establishing parameters for appropriate marketing methods. In addition, the SC is responsible for analyzing clinical literature, both published and unpublished, as it becomes available to the coordinating

center. This is done to assure that the study design and the outcomes measured are based on the compilation of all current evidence regarding LVRS.

Detailed plans for the therapeutic management of patients in all arms of the study were developed by the SC prior to the initiation of the trial, but all arms will include intensive pulmonary rehabilitation. Follow-up exams including history, physical, pulmonary function tests, exercise tests and quality of life assessments will be based on their date of randomization and will occur after rehabilitation at regular intervals as specified in the study's protocol.

A unique feature to all studies sponsored by the NIH is the Data Safety Monitoring Board (DSMB). The DSMB is established by and advisory to the NHLBI. Its major responsibilities are to review and to approve the study's protocol. Additionally, the DSMB will monitor patient safety, study progress, data management and analysis as well as the study's outcomes. If the DSMB finds that the data from the study reveals that the risks or benefits of the study have been clearly and unquestionably proven, it can recommend that the study be modified or terminated. At that time, HCFA may modify its national policy to accommodate the DSMB's recommendation.

Medicare Coverage of Services Furnished in Compliance with the NETT Protocol

Medicare's national policy for LVRS may be found in the CIM at section 35-93, which is entitled Lung Volume Reduction Surgery (Reduction Pneumoplasty, Also Called Lung Shaving or Lung Contouring) Unilateral or Bilateral by Open or Thoracoscopic Approach for Treatment of Emphysema or Chronic Obstructive Pulmonary Disease-NOT GENERALLY COVERED. Currently, this policy states that HCFA has determined that LVRS is reasonable and necessary only when it is provided under the conditions detailed by the protocol of the NETT study for the subset of patients who will be randomized. As a result, Medicare will cover LVRS only when provided to a Medicare beneficiary under the protocol established for this study. Coverage will be provided where the care is furnished in facilities that are approved as meeting the criteria established by HCFA and NHLBI for the NETT study.

Medicare will provide coverage to those beneficiaries who participate in the randomized trial for all services integral to the study and for which the Medicare statute does not prohibit program payment. This includes tests performed to determine whether a beneficiary qualifies for randomization, LVRS and follow-up services that are necessary during participation in the randomized study. However, Medicare will not provide coverage for those services that are prohibited by statute. For example, Medicare will provide coverage for pulmonary rehabilitation and pulmonary function testing, but will not provide coverage for oral steroids because they are self-administrable drugs, and thus, statutorily excluded from coverage.

Potential Modifications to Medicare Coverage of LVRS

The agreement between HCFA and NHLBI details several contingencies that apply to future modifications of Medicare coverage policy. All such modifications will be prompt and based on conclusive data regarding the risks and benefits of LVRS as it becomes available. Until such modifications are made, HCFA will pay for LVRS after the recruitment goals have been met in those centers who continue to comply with the NHLBI-approved protocol and manual of operations. The following are specific situations that may call for an appropriate coverage response:

> If the recruitment goals have been met and the current data establish a benefit of LVRS to a subset of emphysema patients, HCFA will consider adopting a coverage policy for LVRS at the participating centers restricted to this subset of patients and randomization will cease. Expansion to other centers could also be considered.
>
> If the recruitment goals have been met and the current data establish a benefit of LVRS to all emphysema patients considered, HCFA will consider a coverage policy with any limitations or conditions consistent with the evidence.
>
> If the recruitment goals have been met and the current data establish adverse effects of LVRS, HCFA will consider a noncoverage policy for LVRS and randomization will cease.
>
> If the recruitment goals have been met and the current data remain inconclusive as to the risks and benefits or LVRS, HCFA will continue reimbursement only in the context of a continued study protocol including randomization if necessary.

It is important to note that coverage could be modified at any time during the study, even prior to recruitment goals being met, if data are considered conclusive with regard to the risks and benefits of LVRS. HCFA, along with NHLBI and the DSMB will monitor continuously the data so that any warranted changes will be made rapidly.

A REVIEW OF RECENT EVIDENCE CONCERNING LVRS

Some of the concerns expressed about Medicare coverage and the NETT are related to the increasing number of new publications concerning LVRS and how such new data might influence future decisions. The agreement between HCFA and NHLBI assure that these issues can be handled both scientifically and in an expeditious manner. Through the work of the Steering Committee, the NETT protocol already reflects peer assessment of the latest available data, both published and unpublished. Moreover, the contingencies established by the agreement and detailed in a previous section assure that Medicare coverage can be modified rapidly in response to scientifically conclusive new evidence. However, given the large number of new publications concerning LVRS, some of the concerns about the study and its implications for Medicare coverage are understandable. In the following section we analyze the new published evidence and its implications for Medicare coverage.

Criteria for Reviewing Recently Published Studies on LVRS

While there is no universally accepted framework for systematically reviewing clinical evidence, there is a growing consensus that particular criteria guide such reviews. These criteria address several important aspects of how clinical studies are designed and are intended to answer a basic question: Is there sufficient evidence to draw a conclusion about how a treatment affects health outcomes? The following criteria are used to assess whether the most recent evidence is sufficient to draw conclusions about the relevant outcomes of LVRS and hence, carefully evaluate its risks and benefits for Medicare beneficiaries:

1) Were the appropriate outcomes for the procedure studied?

A systematic review should determine the strength of the evidence for drawing inferences about the effect of an intervention on patient outcomes. Therefore, the appropriateness of the outcomes chosen for analysis in clinical studies is key to evaluating the validity and applicability of the results. The most appropriate outcomes to measure must be determined for each intervention based on several factors including: the type of intervention; its expected pathways for affecting the target illness or symptoms; the relevant characteristics and natural course of the illness; and the prognostic factors relevant to the patient population affected.

Outcomes can be classified into two broad categories: health outcomes and intermediate, or surrogate outcomes. The latter are generally clinical measures such as blood pressure, hematocrit, or bone density. Health outcomes measures reflect factors that directly result from a person's health status such as morbidities (and the associated use of medical care services), survival, quality of life, functional status and performance of activities of daily living.

In assessing whether an intervention is effective, there are a number of reasons to more strongly weight studies that measure health outcomes. Most importantly, these measures better reflect the patients experience with the intervention and are therefore advantageous in helping both patients and physicians in balancing the benefits and risks of a therapy. Intermediate or surrogate measures are important in a supporting role for assessing a technology because they help determine the causal pathways along which an intervention works. These measures, in select circumstances, substitute for final outcomes on the assumption that they are predictive of such outcomes -- e g, measured reductions in cholesterol level are expected to correlate with reductions in cardiac deaths -- but these cases are limited. Indeed, several cases are now documented in which changes in intermediate measures either did not result in any change in health outcomes, or resulted in adverse changes (3).

2) Was the type of study used appropriate for drawing inferences about the outcomes of interest?

Almost uniformly, systems designed to evaluate medical evidence rank randomized trials as providing the strongest evidence regarding the impact of a treatment on health outcomes. Many

factors other than the treatment itself may be associated with the measured affect of a treatment. The randomized design provides the strongest method for assuring measured outcomes can be attributed to the treatment as opposed to other factors that might be systematically associated with selection to the treatment. Medical literature cites a growing number of treatments that randomized studies have demonstrated to be either ineffective or harmful after these services had been accepted into medical practice based on data from less rigorous study designs (2, 4).

HCFA strongly prefers data from randomized studies as a basis for its coverage decisions. HCFA does, however, recognize that such studies are not always feasible or ethical and that some decisions can be made based on data from other types of clinical studies. Such decisions are made after due consideration is given to numerous factors such as the risks to Medicare beneficiaries of reimbursing services based on data from less rigorous studies.

3) How were patients selected for the study?

A detailed explanation of how patients were selected for the study and reporting of results is critical to being able to assess the validity of evidence, particularly in the context of making coverage and clinical practice decisions. Careful explanations of selection criteria are necessary for comparing data across studies and in generalizing the results of studies to standard practice settings. This issue is particularly important to the assessment of non-randomized studies since factors that influence selection may also be associated with the measured treatment effect. Moreover, it is critical to understand selection factors if those patients whose data are reported are only a subset of all patients that were treated. For example, when a case series is presented it is important to report whether the patients were consecutive or selected in another manner. Finally, it is important that any changes in selection criteria that occurred during the study be explained.

4) Was the follow-up for the study complete and consistent, and over a time period sufficient to evaluate important outcomes?

The validity of any study depends on the ability to account for all patients over an appropriate time period. As the number of patients lost to follow up increases, the potential for biased results becomes greater. It is possible that patients that cannot be followed are substantially different from those with complete data, potentially resulting in incorrect conclusions regarding the therapy. Thus, studies should be evaluated in terms of their ability to produce complete follow up data. Moreover, reasons that some patients cannot be followed-- e.g., insufficient time from provision of the intervention being studied -- should be detailed carefully, as well as any differences in prognostic factors that might exist between these patients and those with complete data.

The length of the follow up period is also critical and will depend on the type of intervention and over what time period the appropriate patient outcomes are expected to occur. For example, if antibiotic therapy is being studied, outcomes such as resolution of infection might be measured

over a very short time period. On the other hand, technologies that are intended to affect quality of life and mortality may require a longer time frame for adequate study. The longer time frame may be particularly necessary when the durability of benefits is an issue, some risks and benefits would not be apparent until well after the intervention, or natural history data are insufficient to guide expectations about the profile of risks and benefits to be expected.

Reported Outcomes

We reviewed 26 published studies for this report focusing on those that provide data not available for inclusion in the April 1996 CHCT technology assessment. One of these articles was published as the result of a workshop sponsored by NHLBI (5). Since this article does not report or review outcomes data on LVRS, it was not included in the tables attached to this report. We would also like to note that during final editing of this report, we became aware of two additional articles (6, 7). We reviewed the data in these articles and found that they did not change the basic conclusions we reached when we analyzed the other clinical literature. For this reason, as well as the time constraints involved in releasing this report, we did not include these two articles in the summary tables found at the end of the report.

The case series we reviewed are summarized in the tables entitled Comparison of Critical Study Characteristics (Table 1), Key Outcomes Reported (Table 2), Length of Follow-up and Percentage of Patients Achieving It (Table 3), the Forced Expiratory Volume in One Second (FEV1) Follow-up (Table 4), and Six Minute Walk Test (6MWT) (Table 5). Of the literature reviewed, 18 presented original data and report similar measures of lung function. These measures are reported at various time intervals; 10 of the 18 are reported at multiple time intervals.

All of the 18 studies reporting original data measured the forced expiratory volume in one second (FEV1). FEV1 measures in liters the amount of air a patient expires in one second when he or she is blowing out as hard as possible. As can be seen from Table 2, FEV1 is reported at various time periods following surgery in these studies. For those reporting at 3 months, increases in average FEV1 ranged from 33% - 68%. It should be noted that the baseline values from which these percentages are calculated vary considerably -- from a low of .41 to a high of .82. From those studies reporting at both 3 and 6 months, it appears that there is little further change in FEV1 between these periods. Some show modest increases between 3 and 6 months, others show modest declines. Data to compare changes between 6 months and 1 year post-surgery are only provided by a handful of studies. These seem to indicate a maintenance of the initial reported improvements in FEV1 for the few patients available.

Another end point used in several of the studies was forced vital capacity (FVC). FVC measures in liters the total amount of air a patient expires in one breath. Fifteen of the 18 case series used this as a measure of pulmonary function. For the studies reporting at 3 months post-surgery, improvements in average FVC range from 12% - 40%. From those studies reporting at 3 and 6 months, there appear to be further modest improvements in this measure. Again, at 12 months

these improvements seem to be maintained, but very few of the patients were available for assessment of FVC at that time period.

A third pulmonary function test used to evaluate the affects of LVRS is residual volume (RV). RV, which is also measured in liters, records the amount of air left in the lung after the patient has fully expired a breath. This test is unique because it is inversely proportional to the other pulmonary function measurements. A decrease in RV means that the patients' pulmonary function has improved, whereas FEV1 and FVC increase in value when improvement has occurred. Fewer of these studies reported RV relative to the other end points, particularly at multiple time periods. The data available suggest 3 month improvements of 25% - 30%. In contrast to the other measures, the limited data implies reversal of these improvements between 6 and 12 months post-surgery.

A fourth end point used was the six minute walk test (6MWT). The 6MWT measures the distance a patient can walk in six minutes and improves with rehabilitation. This measure of exercise capacity was used in 10 of the 18 studies. Three month increases in 6MWT --a measure for which baseline values varied considerably -- ranged from 13% - 60%. Again, very limited data suggest a maintenance or further improvement in this outcomes at later time periods. It is not clear how much of the improvement in 6MWT is due to rehabilitation, not just surgery.

Other end points were also used in an attempt to quantify improvements in patients who underwent LVRS. Various QOL measures and dyspnea scales were used in these studies. Although these tools can provide valuable patient information, it is difficult to assess these findings in the aggregate because the studies used different scales to measure outcomes. In terms of dyspnea scales, 10 of the 18 clinical studies reviewed for this report used at least one mechanism to record the level of breathing difficulty in the patients studied. Six of the 10 used a single dyspnea scale; two studies used the Mahler Dyspnea Scale (MDS), while the other four studies independently used the Borg Scale, Fletcher's Dyspnea Scale , the Transitional Dyspnea Index (TDI) or the Medical Research Council Dyspnea Scale (MRC). Four studies used two scales in reporting results. Two of these used the MDS and the MRC while the other used the TDI and the MRC and the Borg and the MRC, respectively.

In the 1960's, Borg developed a category scale for ratings of perceived exertion. Borg modified this scale in 1970 in order to increase linearly with the exercise intensity for work on a cycle ergometer. Further modifications were made in 1980 and studies were published revealing the new rating scale constructed as a category scale with ratio properties. The Borg scale, in combination with other mechanisms to measure dyspnea, was used in three of the studies reviewed.

Another measurement of breathlessness used is the Mahler dyspnea scale. This mechanism uses a questionnaire that is administered by an interviewer who has been provided with basic instruction. Three domains of dyspnea are evaluated magnitude of task, magnitude of effort and functional impairment. At the time of the baseline evaluation, the domains are each scored in integers from 0

to 4, with the lower number representing the greater breathlessness. In total, five studies used the Mahler dyspnea scale in the evaluation of patients' breathlessness.

It should be noted that one study used a version of the Mahler scale that was modified by Stoller et al. Stoller and his colleagues modified the Mahler scale in order to "improve the effectiveness and scope of the assessment." However, this modification resulted in a more complicated questionnaire. One disadvantage of the Mahler scale and the Stoller modification is that these measurements are only concerned with dyspnea and do not assess other aspects of COPD.

Several studies also used the Medical Research Council (MRC) Dyspnea Index. MRC is actually two different measures: the MRC respiratory symptoms questionnaire, which was developed by Fletcher, and the modified MRC Dyspnea Index. The Fletcher questionnaire addresses dyspnea, cough, sputum production and wheezing. A disadvantage of this measure is that the scenarios presented to the patient ignore issues such as emotion and mastery of disease. However, the modified MRC, which consists of a single question addressing dyspnea, is even more limited.

In addition to reporting pulmonary function testing and dyspnea scoring, 13 of the 24 studies recorded mortality and morbidity associated with those patients undergoing LVRS. The most common complication was prolonged air leaks, which was reported in ten of the studies reviewed. The percentage of patients suffering from prolonged air leaks according to these studies ranged from 11% to 77%, with a median of 45.5%.

The second most frequently recorded complications were pneumonia, perioperative death and non-perioperative death; each of which appeared in seven of the clinical studies. Those suffering from pneumonia ranged from 5% to 17%, with a median of 11%. Perioperative death ranged from 2% to 8%, with a median of 4%, while non-perioperative death ranged from 6% to 17% with a median of 10%.

Other morbidities were recorded less frequently in the scientific literature. Complications arising from infection were documented in four of the studies and pulmonary embolism appeared as a morbidity in three of the studies. Myocardial infarction, tension pneumothorax, cardiopulmonary instability, gastrointestinal complications, tracheostomy, prolonged ventilator dependence and reoperation were listed as complications in two studies. Those morbidities that were documented in a single study include bleeding, prolonged ileus, late spontaneous pneumothorax, severe and minor adhesions, ischemic stroke, neurological difficulties, prolonged chest tube drainage, diaphragmatic paralysis, empyema, cardiac arrest, fecal perforation and bleeding into the pleural tent.

Analysis and Evaluation of Published Data

In the following sections, the reported outcomes in these studies are analyzed with respect to the inferences that can be drawn about the risks and benefits of LVRS, as well as the relevant policy implications.

Appropriateness of Reported Outcomes

The range of outcomes that would be necessary to fully evaluate the effectiveness of LVRS -- that is, provide the appropriate evidence about its risks and benefits for patients, physicians and health plans to make informed decisions -- is determined by a number of factors. First, LVRS is a palliative surgical procedure that removes nonfunctioning lung tissue in order to improve lung function (establish more normal breathing patterns) and reduce dyspnea. It is targeted to patients whose lung function is already substantially impaired by emphysema. COPD due to emphysema is a chronic disease with a natural history of continuous deterioration of lung function. Its physical effects include dyspnea (chronic shortness of breath) which reduces energy and vitality, and which can lead to anxiety, dependency, loss of self-esteem, and other psychiatric and psychosocial problems. All of these effects, along with restricted activity due to fear of attacks, can substantially diminish health-related quality of life. COPD is also associated with increasing morbidity, disability, and mortality -- the latter particularly affecting patients over the age of 65.

It is clear that selected lung function and dyspnea measures, as have been reported in the vast majority of published studies, are necessary to evaluate LVRS. Given the above profile, however, careful and comprehensive evaluation of LVRS would require accurate measurement and reporting of additional outcomes such as exercise tolerance, health - related quality of life, morbidity, medical care service use and mortality for the following reasons:

- The overall objective for LVRS is improved quality of life, which can now be measured on several general and disease-specific scales. For patients to fully evaluate and compare benefits and risks, it is important to ascertain whether improvements in clinical measures of lung function (e.g. FEV1) and in dyspnea scales result in improved quality of life factors such as physical, social and psychological functioning. While lung function and quality of life measure may indeed be correlated, the causal link has not been well established in the medical literature

- Given the nature of the procedure, it is critical to document morbidity/mortality profiles. The natural disease process for those patients that might be selected for LVRS is likely to include extensive and increasing morbidity and mortality rates. Surgery entails immediate risks in terms of procedure-related mortality and other complications. While such risks are often considered as being relevant to the period during and immediately following surgery, it cannot be ruled out that there are longer run risks in terms of the procedure adversely affecting the morbidity/ mortality profile natural to these patients. Likewise, a benefit to the surgery might be an improvement in this profile. These risks and benefits are important for patients to evaluate for their care decisions, and such information can only be available if all the appropriate outcomes are measured.

- A full range of measures is also important so that intermediate outcomes such as

lung function measures can be correlated with final outcomes such as quality of life. Such analyses would help to assure that reported improvements in intermediate measures, as well as dyspnea and exercise tolerance measures, had appropriate clinical causation and were not due to placebo or supervision effects. Of equal importance, correlation and other multi-variate analyses can help detect meaningful thresholds for improved outcomes and be useful for developing selection criteria for the procedure. For example, it may be useful to determine whether patients that do not have improved quality of life can be distinguished from those that do by a threshold improvement in a measure such as FEV1. In addition, baseline characteristics of patients in published studies have varied considerably so that large post-surgery percentage increases in FEV1 and other measures in some studies result in values that are smaller than the pre-surgery values in other studies. Comparing the quality of life impact of such changes from varying baselines would also be helpful for developing selection criteria.

While some reporting of all of the important outcomes can be found within the original studies reviewed, only one study reports the full range of measures. All of the studies include lung function measures such as FEV1 and FVC, and many include a dyspnea scale and a measure of exercise tolerance. Only one study comprehensively attempts to measure health related quality of life through a recognized instrument. None of the studies provide an extensive correlation analysis among the key outcomes.

Thus, our ability to evaluate the risks and benefits of LVRS using current evidence is significantly compromised by the lack of quality of life data. Quality of life is the major objective of LVRS and therefore, should be the most critical factor considered in assessing this procedure. The one study that measured quality of life found that pulmonary rehabilitation provided during the pre-surgical period improved selected quality of life factors, while the surgery itself improves additional factors (21). It also found that overall quality of life six months post surgery had significantly improved relative to six months before surgery. While this finding is important in terms of suggesting a benefit from the surgery, how much of the measured improvement can be attributed to the surgery as opposed to the pulmonary rehabilitation services and other factors cannot be determined from these data.

In addition, the various dyspnea scales and exercise tests reported provide important information about LVRS, but are not adequate surrogates for assessing changes in health-related quality of life. Dyspnea scales subjectively measure a symptom of COPD, but not the associated limitations on functioning that affect quality of life. Moreover, a variety of dyspnea measures are used among the studies reviewed. Their relative reliability and validity is uncertain, and comparability across the measures is impossible. Exercise tolerance outcomes, such as the six minute walk test, do reflect an aspect of physical functioning. These tests measure a patients performance under clinical supervision which may in itself improve performance (e.g. distance walked), however. More importantly, how a patient performs under such supervision may not reflect their willingness

to function in daily activities outside the clinical setting. Moreover, what increase in distance walked is clinically significant to the patient (apart from being statistically significant) is unknown. Indeed, reported distances both at baseline and post surgery vary considerably among the studies.

Our ability to assess the risks and benefits of LVRS is also limited because most of the studies report their outcomes in terms of average changes. While it is useful to know the direction and magnitude of change on average, it is equally if not more important to know the distribution of those changes-- that is, the probability of achieving a change of a particular magnitude in an outcome measure. Patients, physicians and health plans can better assess a procedure when they know what percent of patients had little or no improvement, what percent had improvements close to the average and what percent had very large improvements. Indeed, the limited amount of disaggregated data available in these studies and in the CHCT study suggest a significant number of patients that have little or no improvement in some outcome measures.

Study Design

All of the published data reviewed were from observational studies called case series. That is, results were reported for a series of patients that underwent LVRS. There were no published studies that compared -- either in a randomized or nonrandomized manner -- patients undergoing LVRS with similar patients treated by other methods. Therefore, the reported outcomes may suffer from several biases. Drawing inferences about the effectiveness of LVRS from these data requires considerable caution. For example, some observed effects may be due to how patients were selected to surgery rather than the surgery itself. As will be discussed below, these biases may be exacerbated by other problems such as incomplete follow-up and lack of clear selection criteria.

Case series data can provide useful information about the effectiveness of a procedure, however, when patients serve as their own control group. That is, patients' experience before and after the procedure can be compared to draw valid inferences about the procedure. Such comparisons can be made under the following conditions if the measured impact is of significant size, it is unlikely the observed effect could be attributed to other causes; and a good natural history (a detailed record of health experience) exists for similar patients to act as a comparison. Because the first two conditions can be met for some outcomes reported in existing LVRS studies, the ability to achieve certain surgical objectives and particular risk and safety issues associated with achieving these objectives can be established to some extent by these data. In particular, it can be concluded that some patients undergoing LVRS will realize improvement in selected lung function measures such as FEV1 for at least a short period of time.

On the other hand, there are a number of critical issues concerning the risks and benefits of LVRS that cannot be resolved by these case series. First, it is not clear that the first two conditions can be met for exercise tolerance or quality of life measures because: 1) what represents a clinically significant magnitude of change is less clear, and 2) more importantly, medical care services and disease related factors other than LVRS can have an impact on these measures. For this reason,

the relative roles of surgery and pulmonary rehabilitation in producing reported improvements in quality of life and exercise tolerance cannot be accurately determined with current data. Making such a determination will require a controlled study.

Most importantly, critical questions about the impact of LVRS on morbidity and mortality of COPD patients can only be evaluated accurately by a randomized study. Although extensive morbidity and mortality is associated with end stage COPD, an adequate natural history has not been documented for patients similar to those receiving surgery. Without such information it is impossible to judge whether the post-surgical mortality and complication rates reported in these studies, or the substantial mortality and hospitalization rates calculated from Medicare data and presented below, have been affected favorably, adversely or not at all by the procedure.

Duration and Completeness of Patient Follow-up

Another substantial weakness in the studies reviewed is the relatively short time period for which patients were followed to assess both the outcomes that were reported and those that need to be studied. A surgical procedure often includes both immediate risks as well as a substantial recovery period. Thus, in balancing risks and benefits it is critical to know not only that outcomes improve, but how durable are those improvements. Moreover, it is important for the follow-up period to be of sufficient duration to evaluate any longer term risks that might be attributed to the surgery.

There is no gold standard for determining a sufficient follow-up period for the careful and complete evaluation of a procedure, or an appropriate period to guide coverage decisions. Again, the nature of the procedure, illness and patient prognosis need to be considered. For example, patients may want to compare the length of time surgical benefits are maintained to the expected recovery period. It is likely that recovery from LVRS, in addition to pre-surgical evaluation and rehabilitation time, imply that patients would not likely fully realize any quality of life benefits for 3-6 months. Existing data imply that lung function and exercise tolerance measures tend to peak at six months and then level off or decline. Therefore, a time frame of 12-24 months would seem reasonable in order to assess LVRS and provide useful information to patients. Moreover, this is likely to be a reasonable period in which to evaluate the impact of LVRS on the morbidity/mortality profiles of these patients.

In contrast, outcomes for most patients in the published studies are reported for relatively short periods following surgery. The denominators calculated for Table 3 represent the number of patients receiving LVRS in studies that report outcomes at various time intervals. While 535 and 584 patients were reported at studies presenting data at 3 and 6 months respectively, only 364 were in studies reporting data at one year. Only a handful of patients had data reported for periods in excess of one year. Cooper et. al. report data based on their initial 20 patients all of whom were a minimum of 24 month postsurgery. It is not clear from the published study, however, how many of the 20 patients were actually followed for purposes of calculating the reported outcomes.

Perhaps the most significant flaw in these studies with regard to the accuracy and relevance of the estimated changes in outcomes they report is that a substantial number of patients that were provided LVRS could not be followed in order to collect postsurgery data. Thus, important outcomes information is missing for these patients at various time intervals. Table 3 summarizes the completeness of follow-up for the 17 studies presenting original data on consecutive case series. At three months following surgery, 329 of 461 patients (71%) could be followed for the purposes of reporting outcomes. For studies that report outcomes at 6 months, 65% of patients were available for follow-up. For those reporting at 3 and 6 months, 234 of 391 (60%) were available at the latter time. Finally, of the 367 patients in studies that reported outcomes at one year, only 30% (110 patients) were available for follow up.

The high percentage of patients that could not be followed substantially limits the implications that can be drawn from these data about any particular outcome measure, and prohibits reasonable conclusions about the risks and benefits to patients. To the extent that patients that could not be followed differed systematically in terms of outcomes from those that could, any reported change in outcomes would be a biased estimate of the effect on the population studied. For example, patients with the poorest outcomes may be less likely to return to particular facilities for evaluation or respond to questionnaires, biasing estimates to reflect more favorable outcomes than would be true for the population of treated patients. Thus, reported average improvements in FEV1, FVC, RV, 6MWT and other measures might be attributable to LVRS, selection bias due to incomplete follow-up, or both. Moreover, since the percent follow-up declines over time, 6 and 12 month outcomes may reflect greater bias than the 3 month outcomes. Since the studies did not detail the reasons patients could not be followed, or provide any information about differences between patients that were followed and those that were not, an assessment of the magnitude of such bias is not possible.

It should be noted that selection bias as discussed refers to applying or projecting the reported results to the treated or potentially treated population. The reported improvements in some outcomes could be applicable at least to patients similar to those followed (subject to the all other study design issues described in this report). The lack of reported information about these patients, however, precludes identifying this subpopulation.

Patient Selection

Drawing a conclusion about LVRS outcomes is also made more difficult because patient selection criteria are not clearly described. Thus, even if the incomplete follow up issue were not a significant factor, generalizing the published results would not be possible with any accuracy. In other words, it is extremely difficult to compare results across studies, and patient selection criteria cannot be developed with any degree of confidence either to guide medical practice or coverage decisions. Indeed, baseline values for key measures such as FEV1 and the six minute walk test vary considerably among the published studies, indicating there may have been substantial differences among patients reported in the various studies.

Another concern about patient selection is that many more patients have been provided LVRS than are reported in these studies. Because of the variable study selection criteria for patients, it is difficult to know how well-reported patients represent those not included in published series. Moreover, while some studies specifically state that they are reporting consecutive patients receiving the procedure, others have reported only a selected subset of those patients undergoing LVRS.

Supplement: **Analysis Based on Medicare Data**

Among the significant gaps in the data from the published studies are the paucity of good information concerning mortality and morbidity beyond the immediate post-surgical period. Mortality rates beyond this time frame are either not provided, actuarial projections, or potentially subject to substantial\bias due to incomplete follow-up. There are no systematic attempts to examine medical care service use as a proxy for post-surgical morbidity. While administrative data such as claims files are usually not recommended as a primary source for rigorous technology assessment, they can be used as a supplemental data source to fill in such gaps.

In order to provide additional information concerning the outcomes of LVRS, we examined data from the Medicare claims system and the Social Security enrollment files. For patients identified as being provided LVRS, pre- and post-surgical episodes of care were identified and linked to information concerning date of death. These episodes enabled us to directly compare utilization of various hospital related services before and after LVRS, as well as to calculate post-surgical mortality rates at various time intervals. The database included 722 patients for whom claims were submitted that included the ICD9 code for LVRS which became available for the final quarter of 1995. Therefore, most of these patients were provided LVRS between October 1995 and January of 1996.

The episode constructed for each of the patients included all acute care hospitalizations, skilled nursing services, hospital or unit rehabilitation services and long term care services billed for the patient during 1995 and 1996. On average, pre-surgical periods (January 1, 1995 to the date of surgery) were 328 days in length while post-surgical periods (surgery date until December 31, 1996 or the date of death) were 332 days in length. Data related to mortality is current through April of 1997. Deaths were aggregated at 3 month intervals for the purpose of calculating mortality rates.

Chart I details mortality rates following surgery for the 722 patients. At 3 and 6 months post-surgery, mortality rates were 14.4% and 16.9% respectively. Mortality rates increased to 23% and 28% at 12 and 18 months following surgery. These rates are considerably higher than those reported in most of the studies reviewed for this report. Even the one study that included patients classified as high risk reported mortality rates of 18% at one year (17).

Since the procedures that were billed as LVRS represented only a subset of hospitals providing and patients undergoing the procedure, it is possible that these mortality rates may not be

representative of all Medicare eligible LVRS patients. Therefore, we also examined procedures provided in 1994 and 1995 that were likely to have been LVRS, but coded as other surgeries. Specifically, we analyzed bills with a diagnosis code indicating emphysema and using related procedure codes such as those for wedge resection, excision of bullae, and lobectomy. Claims fitting this description were likely to have been for LVRS since they were almost nonexistent in 1992, grew rapidly from 1993-1995 (the years most LVRS procedures were performed) and declined substantially in 1996 after the noncoverage policy was issued. The calculated post-surgical mortality rates for the 1994 and 1995 procedures (representing more than 2000 and 3000 patients respectively) were nearly identical to those calculated for the 722 patients for whom the LVRS code was used, rising to over 20% by one year following surgery. Thus, it is likely that the mortality rates presented on Chart I are closely representative of post-surgical experience for Medicare patients receiving LVRS in these years.

Table 6 compares pre- and post-surgery use of selected medical care services for the 722 LVRS patients. The inpatient stay in which LVRS was provided has been excluded from these calculations. Use of acute care hospitalization increased substantially after surgery. There were 197 stays for 123 patients in the pre-surgery period while there were 304 stays for 160 patients in the post-surgical period. Average days hospitalized increased from 11.8 to 18.7 between the two periods. Long term care and rehabilitation services also increased substantially.

Conclusions from the Data Analysis

We have carefully examined key published articles that represent data that became available following the April 1996 CHCT technology assessment. The review focused on whether conclusions about the outcomes of LVRS for Medicare patients could be drawn from the available evidence. Several evaluation criteria were applied to systematically analyze the data for this purpose including: whether the appropriate outcomes were studied; whether the basic study design was appropriate to answer important questions about risks and benefits; whether patient follow-up was complete and consistent and whether patient inclusion criteria were addressed properly. The general conclusion from this review differs little from that detailed by the CHCT report -- it is not possible to draw scientific conclusions regarding the risks and benefits of LVRS from the available data. Therefore, more careful study of this procedure is necessary before its effectiveness can be determined and criteria developed to appropriately select patient for the procedure.

It is clear that for some patients, selected measures of lung function, dyspnea, and exercise tolerance will improve for at least a brief time period. Given the variability in patient selection across studies and the substantially incomplete follow up of patients, however, it is impossible to identify which patients would benefit in this manner. Where data reporting allowed for analysis, it was clear that a significant number of patients undergoing LVRS did not benefit in terms of substantially improved lung function.

Of greater importance, however, is that the current data do not allow for conclusions to be drawn

about the risks and benefits of LVRS even for those patients that may experience such short term improvements. The durability of reported improvements in these outcomes cannot be determined from the current data. More significantly, whether any such improvements result in increased quality of life or functionality for patients -- the main objective of LVRS-- is unknown. It appears that post-surgical mortality is high and that relative to the period prior to surgery, use of medical care services increases after the procedure. Whether LVRS favorably or adversely affects the morbidity/mortality profile relative to what would be experienced by COPD patients in the absence of surgery cannot be assessed adequately using the published data because of the absence of a control group or good natural history. Table 7 summarizes key unanswered questions concerning the risks and benefits of LVRS and the corresponding weaknesses in existing data.

The Medicare data analyzed for this report underscores the potential weaknesses and biases in the existing case series data and the need for more careful evaluation of LVRS. The fact that mortality rates calculated from the Medicare/Social Security data are considerably higher than rates reported in the literature implies that the improvements in selected outcomes found by these studies may be biased to be more favorable than would be representative of all patients that have had LVRS. Whether the bias is attributable to the incomplete patient follow-up associated with these studies, differences between those cases included in published literature and those not included, or both, these results cannot be generalized to reflect results for any particular population of patients or to select patients that might benefit from the procedure.

CONCLUSION: IS CURRENT MEDICARE COVERAGE POLICY APPROPRIATE FOR LVRS?

Medicare now covers LVRS only when provided under the NETT protocol. HCFA implemented this coverage with conditions approach in April, 1996 after considering the CHCT report, internal examination of data and extensive communications with the medical care and scientific communities. Based on this information, it was decided that this procedure met all the criteria for coverage with conditions that were detailed in the previous section concerning Medicare coverage policy. Essentially, LVRS was considered a potentially promising procedure that was substantially unproven in many regards and therefore, could be covered only under conditions that would provide valuable data to guide future Medicare decisions.

Some have questioned this rigorous approach to Medicare coverage because there have been a number of published articles reporting observational data that seem to indicate effectiveness and several media reports providing anecdotal evidence of dramatic successes. However, the increased quantity of published data does not necessarily fill the existing gaps with regard to critical evaluative questions. The careful examination of the more recent published evidence and the supplemental analysis of Medicare/Social Security data does not change the basic conclusions reached in April 1996 to support the current coverage policy. To the contrary, the analysis presented in this report raises additional questions about the risks and benefits of LVRS that can be answered only by a controlled study.

An unproven procedure might be defined as one for which available data are sufficient to resolve some basic safety and efficacy issues and establish "promise," but not sufficient to answer many critical questions about risks and benefits for patients. Some of the most challenging coverage decisions facing health plans -- whether private or public -- involve unproven procedures. A simple yes or no decision can be inappropriate in these cases. If reimbursement is not provided, development of a potentially valuable treatment might cease. On the other hand, unrestricted coverage can cause rapid diffusion of the procedure without adequate evidence of efficacy and therefore, result in ineffective or harmful care being provided. In addition, coverage and rapid diffusion often preclude the implementation of clinical studies designed to generate necessary medical evidence.

HCFA faced such a challenge with regard to LVRS in 1996. Despite little published evidence, significant risks and disagreements within the surgical community about appropriate technique and patient selection, the procedure spread rapidly from 1993-1995. Continuing a policy of noncoverage might have stopped further development of the procedure and the production of needed information. A coverage policy without carefully structured conditions and limitations may have put many beneficiaries at risk of death or further impairment due to the paucity of information to guide proper patient selection, technique, and support services for LVRS. Moreover, an unrestricted coverage policy would not have resulted in improved study designs and data maintenance. Therefore, the gaps in the medical evidence would have remained to the foreseeable future.

For all of these reasons, Medicare devoted considerable resources in seeking policy alternatives to the yes/no coverage decision for LVRS and other unproven procedures. Specifically, HCFA has sought to develop policies that reimburse for such procedures under conditions that: 1) provide access to beneficiaries in a manner that uses the limited information available to maximize the likelihood that the service can be delivered safely and effectively; and 2) provide the data necessary to direct future coverage decisions.

The NETT represents an excellent opportunity for Medicare to provide coverage of LVRS with these important objectives in mind. The NETT protocol, under which current coverage is determined, was developed by well-qualified members of the pulmonary and thoracic surgery communities, and based on the most recent evidence available concerning the treatment of emphysema. Medicare reimbursement under this protocol will provide access to state of the art health care for thousands of beneficiaries. The study is designed so that the data that are now lacking will be available in the near future to draw conclusions about critical risks and benefits of LVRS for Medicare beneficiaries and effectively guide future coverage policy. Most importantly, Medicare's participation in the NETT is structured so that coverage of LVRS can be modified rapidly and as frequently as needed to respond to conclusive data as it becomes available.

Some concern has been expressed over two features of the NETT and its relationship to Medicare coverage policy: first, that it employs a randomized design, and second, that it excludes laser and unilateral approaches to LVRS. Those concerned with the randomization believe the procedure is

effective, and therefore consider placing patients in the maximal medical therapy arm of the NETT to be unethical. The randomized design is both scientifically valid and medically ethical for two reasons: current data do not establish relative superiority or inferiority of any treatment in the study; and no other study design will provide conclusive answers to the many questions about LVRS that are critical to medical practice, patient choice and coverage policy. The NETT's exclusion of unilateral and laser techniques reflects both existing data regarding relative efficacy and surgical consensus that bilateral excision techniques are the preferred modalities. Some believe that the other approaches may have secondary roles in the treatment of specific patients who cannot undergo the bilateral procedure. When, and if, the basic effectiveness of the bilateral excision approaches is established, the adjunctive role of other procedures will be examined for Medicare coverage.

In conclusion, after comprehensive examination of recent published and unpublished evidence regarding LVRS, the careful and flexible approach of providing coverage under the NETT protocol remains the appropriate course of action for the Medicare program on behalf of its beneficiaries. The data generated by the NETT potentially will improve treatment for hundreds of thousands of Medicare beneficiaries suffering from emphysema as well as advancing the state of the science for all individuals suffering from this disease. Moreover, to the extent that LVRS is demonstrated as effective, the results will guide patients to this procedure who may experience benefit and will steer away those patients for whom LVRS would be ineffective or harmful. HCFA will continue to fulfill its responsibility to monitor new data concerning LVRS, whether from the NETT or other sources, and modify coverage policy accordingly.

Table 3. Length of Follow-up and Percentage of Patients Achieving It

First Author	Less Than Three Months	Three Months	Six Months	Twelve Months	Greater Than Twelve Months
Naunheim		25/50			
Criner	3/3	3/3	3/3 (5 Months)	1/3 (10 Months)	
Bingisser		20/20			
Gaissert		10/33	7/33		
Zenati		30/35			
Roue+			13/13	10/13	6/13 -- 2/13 (up to 48 Months)
Kotlo...			90/120 (3-6 Months)		
Gelb			10/14	10/14	
O'Donnell		8/8			
Miller	40/53	40/53	40/53		
Argenziano**		55/85	35/85		
Eugene***	43/44	40/44	38/44	18/44	
Gelb			12/12 (5-6 Months)		
Yusen		53/84	37/84	19/84	
Cooper			101/150	56/150	
Sciurba****		20/20			
Cordova*****		25/26	13/26	13/26	
TOTALS	86/100	329/461	362/553	108/250	6/13 to 2/13

* For FEV1, 13 of 13 were followed to 6months; 9 of 13 to 12 months; 7 of 13 to 18 months; 6 of 13 to 24 months; 5 of 13 to 36 months; and 3 of 13 to 48 months
For TLC, 7 of 13 were followed to 6 months only.
For PaO2 and PaCO2, 13 of 13 were followed to 6 months; 8 of 13 to 12 months; 6 of 13 to 18 and 24 months; 3 of 13 to 36 months; and 2 of 13 to 48 months.
For FS, 13 of 13 were followed to 6 and 12 months; 12 of 13 to 18 months; 10 of 13 to 24 months; 6 of 13 to 36 months; and 3 of 13 to 48 months

** This articles does not contain a chart summarizing this data.

*** Emphysema surgery on 152 patients (did not specify whether they received LVRS or another procedure). Results are reported on 44

**** This article does not specify in the text or on the chart at what time interval follow-up occurred

***** Follow-up for the 6MWT was done on 12 patients at baseline, 3, 6 and 12 months post-operatively.

NOTE: Although the McKenna article reports original data, it is not included in this summary table because it does not specify at what time interval post-operative results are recorded.

NOTE: Patients reported by Yusen were included in the totals only at three months because it was assumed that the patients were identical to those reported by Cooper

Table 4. Forced Expiratory Volume in One Second (FEV1) Follow-up

First Author	Less Than Three Months	Three Months	Six Months	Twelve Months	Greater Than Twelve Months
Naunheim		25/50			
Criner		2/3			
Bingisser		20/20			
Gaissert		10/33	10/33		
Zenati		30/35			
Roue			13/13	9/13	
Kotloff*			90/120		
Gelb			10/14	10/14	
O'Donnell		8/8			
Miller	40/53	40/53	40/53		
Argenziano		9/85			
Eugene	43/44	40/44	38/44	18/44	
Gelb			12/12 (5-6 Months)		
Yusen		53/84	37/84	19/84	
Cooper			101/150	56/150	
Sciurba**		20/20			
Cordova		25/26			
TOTALS	83/97	282/461	314/439	92/221	

* Unspecified between three and six months.

** Table does not specify the time interval after surgery these results were recorded. However, the graphs in the article are all based on 3-month post-operative data.

Table 5. Six Minute Walk Test (6MWT) Results

First Author	Three Months	Six Months	Twelve Months	Greater Than Twelve Months
Naunheim	15/50			
Criner	N/A			
Bingisser	20/20 (12 MWT)			
Gaissert	10/33	10/33		
Zenati	30/35			
Rou	N/A			
Kotloff*		90/120		
Gelb	N/A			
O'Donnell	N/A			
Miller	40/53	40/53		
Argenziano**	9/85	9/85		
Eugene	N/A			
Gelb	N/A			
Yusen	52/84	38/84	19/84	
Cooper		101/150	56/150	
Sciurba***	20/20			
Cordeva	12/26	12/26	12/26	
TOTALS	158/406	300/551	87/260	

* Unspecified between three and six months.

** This data represents patients with concomitant tumors who underwent LVRS.

*** Table does not specify the time interval after surgery these results were recorded, however the graphs are all based on 3-month post-operative data

TABLE 6
USE OF SELECTED MEDICAL CARE SERVICES
BEFORE AND AFTER LVRS

	Pre-Surgery			Post-Surgery		
	Number	Stays/Patient [a]	Average Days [b]	Number	Stays/Patient [a]	Average/Days [b]
Acute Care Hospital	197	1.6	11.8	304	1.9	18.7
Long Term Care Facility	7	2.5	33.7	60	3.4	42.6
Rehabilitation Hospital	10	1.7	21.6	37	2.3	24.2
Unit Rehabilitation	4	1.5	20.0	51	1.3	17.5
Skilled Nursing Facility	10	1.7	19.4	118	1.8	25.2

a) Stays per patient using the particular service.

b) Average number of days in each facility for patients using the service

c) Inpatient rehabilitation units in acute care hospitals

NOTE: There were an average of 328 days per patient in the pre-surgery period and 332 days in the post-surgery period.

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Table 1. Comparison of Critical Study Characteristics†

Study	Type	# of Patients	Patient Traits	Follow-up (months)	% of Patients Followed	Procedures Studied	Complications (with percentages where applicable)	Outcomes Measured
Naunheim, et al.	Prospective case series	50	34 Male, 16 Female Age-- Mean: 61.5 Range: 31-78	3	24-50	Unilateral VATS	PAL 30% Bleeding 6% Pneumonia 6% Reintubation 6% PI 4% OM 4% MI: 2%	FEV1 FVC PO2 tension RV 6MWT MDS
Criner et al	Case series	3	1 Male, 2 Female Age-- 53, 53, 60	3-5	100	Bilateral thoracotomy Bilateral median sternotomy	PAL TP	FVC FEV1
Bingisser, et al.	Prospective	20	15 Male, 5 Female Age-- Mean: 64 Range: 42-78	3	100	Bilateral VATS	Severe adhesions 10% Minor adhesions 30% CT 10% TP 5% Reintubation 5%	FEV1 RV 12MWT FVC TLC IVC RV/TLC
Gaissert et al.	Retrospective analysis	33	Age-- Mean: 57	3 6	30 21	Bilateral median sternotomy		FEV1 6MWT PO2 MDS

Study	Type	# of Patients	Patient Traits	Follow-up (months)	% of Patients Followed	Procedures Studied	Complications (with percentages where applicable)	Outcomes Measured
Zenati, et al.	Case series	35	21 Male, 14 Female Age-- Mean: 57.8+/- 7.2 Range: 39-68	3	86	Unilateral thoracoscopy. Bilateral thoracoscopy. Bilateral median sternotomy	PAL 77% Pneumonia 17% Reintubation 6% Empyema 3% Pl 3% Superficial Inf 3%	FEV1 FVC RV MVV 6MWT Borg Scale PaCO2 MDS
Roue et. al.	Retro-spective case series	13	12 Male, 1 Female Age-- Mean: 55 Range: 42-70	6 12 18 24 36 48	100/100/54* 69/62** 54/46** 46/46** 38/23** 23/15**	2-bilateral(1-MS, 1 thoracotomy) 11-unilateral, unspecified approach	30 day POM 8% 48 month POM 8% PAL 46% IS 8% PE 8% Inf 8%	FEV1 PaO2 PaCO2 TLC FS
Kotloff, et al	Case series	120, 80 bi-lateral MS; 40 VATS,	Age-- Mean: MS -- 62.4+/-6.9 VATS -- 59.3+/-9.4		MS: 70 VATS: 85	Bilateral MS Bilateral VATS	MS-- OM 4% THM 14% Reintubation - 18% VATS-- OM 3% THM 3% Reintubation - 3% Total PAL - 11%	FEV1 FVC RV 6MWT

Study	Type	# of Patients	Patient Traits	Follow-up (months)	% of Patients Followed	Procedures Studied	Complications (with percentages where applicable)	Outcomes Measured
Gelb, et al	Case series	10	10 Males 0 Females Age-- Mean: 67+/- 8	6 12	71	Bilateral thoracoscopy and bilateral VATS		FEV1 FVC RV VC DcO PS1AT TLC
O'Donnell, et al		8	8 Males 0 Females Age-- Mean: 64+/-2	3		Unilateral MS	PAL 38% Pneumonia 13%	FEV1 FVC TLC RV FRC TDI MRC
Miller, et al.	Case series	53	36 Males, 17 Females Age-- Mean: 67 Range: 55-75	1 3 6	75	Bilateral MS and unilateral thoracotomy	OM 2% Late death 8% PAL >7 days 40% PAL >14 days 26% Reintubation 17% Arrhythmia 21% GI 15% Pneumonia 17% Inf 9% Neurologic (transient) 19% Tracheostomy 13% Wound Inf 2%	FEV1 FEV1/FVC FVC MVV PO2 PCO2 6MWT

Study	Type	# of Patients	Patient Traits	Follow-up (months)	% of Patients Followed	Procedures Studied	Complications (with percentages where applicable)	Outcomes Measured
Argen-ziano	Pro-spective trial	85	35 Males, 50 Females	3 6	11 11	Bilateral MS	30 day OM 7%	FEV1 FVC 6MW1 MRC
Eugene, et al	Pro-spective	44	28 Males, 16 Females Age-- Mean: 66	1 3 6 12	98 91 86 41	Unilateral VATS - 34 Bilateral VATS - 6 Bilateral MS - 4	PAI: 36% GI complications 18% Add'l deaths within 1 year 11% Add'l deaths within 60 operative days 5% Pneumonia 5% Perioperative death 2% PVS 2% PE 2%	FEV1 FVC RV TLC Borg MRC
Gelb, et al.	Pro-spective case series	12	10 Males, 2 Female Age-- Mean: 68+/- 4	5-6 12	100 25	Bilateral VATS		FEV1 FVC RV TLC FRC SGaw DLCO
Mc-Kenna, et al.	Case series	11	8 Males, 3 Females Age-- Mean: 69.4	Not specified	91	Thoracoscopic LVRS for lung cancer	PAI: 45% OM:4%	FEV1

Study	Type	# of Patients	Patient Traits	Follow-up (months)	% of Patients Followed	Procedures Studied	Complications (with percentages where applicable)	Outcomes Measured
Yusen, et al. ***	Case series	84	44 Male 40 Female Age-- Mean: 60+/-9	3 6 12 Dyspnea-- 3 6 12	63 44 23 54 36 20	Bilateral MS	Prolonged chest tube drainage 63% Pneumonia 11% Reoperation 10% OM 6% PVS 4% DP 2% PI 1% Empyema 1% Wound inf 1%	FEV1 FVC RV TLC Pao2 6 MWT MRC MDS
Cooper, et al ***	Case series	150	Age-- Mean: 61 Range: 36 - 77	6 6,12	67 55	Bilateral MS	PAL 46% 6-mth mortality 15.3% Pneumonia 11% Mechanical ventilation 7% Reoperation 6% Tracheostomy 3.3% MI 1.3% Cardiac arrest 1.3% Cecal perforation 1.3% Bleeding into pleural tent 1.3%	rFEV1 FVC RV TLC PaCO2 PaO2 6MWT MRC MDS
Sciurba, et al	Case series	20	12 Male 8 Female Age-- Mean: 60 Range: 40-75	Not specified in chart.	100	17 Unilateral laser with staples 3 bilateral MS with staples		6MWT TLC RV FRC FEV1 PaCO2 DCO TDI

Study	Type	# of Patients	Patient Traits	Follow-up (months)	% of Patients Followed	Procedures Studied	Complications (with percentages where applicable)	Outcomes Measured
Cordova et al.****	Case Series	26	10 Male 16 Female Age-- Mean: 58+/-8.7	3 6 12	96 50 50	Bilateral MS		FVC FEV1 TLC RV FRC MVV PaCO2 6MWT
Brenner, et al.	Meta-analysis of procedures	33 unilat. laser 55 unilat. laser. 28 unilat. laser 87 unlat. staples 41 bilat. VATS 20 bilat. median sternotomy	NA	NA		Unilateral laser, unilateral staples, bilateral VATS and bilateral MS		

Study	Type	# of Patients	Patient Traits	Follow-up (months)	% of Patients Followed	Procedures Studied	Complications (with percentages where applicable)	Outcomes Measured
Albert, et al.	Economic analysis of billing records	23	Billing data available	Retrospecti ve study		MS and thoracoscopic approach using laser		LOS Mortality MCC PF SR
Slone, et al.	Review article	NA	NA	NA	NA	Bilateral median sternotomy		LVRS is promising procedure with near immediate improvement in pulmonary function and QOL in select patients. Imaging studies are important in pre-op evaluation and surgical planning. Bilat has demonstrated greatest overall benefit.
Tonelli, et al.	Review article	NA	NA	NA	NA	NA	NA	The purpose of this article is to introduce and disseminate current difficulties, deficiencies and differences of opinion regarding the evaluation of innovative lung therapies.
Naun-heim	Review article					Unilateral bilate ral VATS, unilateral bilate ral MS	Mortality ranged from 0- 18%	FEV1 RV 6MWT O2 Use

† Articles by Brenner, et al and Wisser, et al (29 and 30, respectively on the Reference list) were also reviewed but not added to the Tables because they did not provide any significant additional information.

* FEV1 and TLC, respectively.
** FEVI, PaO2 and PaCO2, respectively.
*** The Yusen and Cooper articles report on the same patients.
**** Follow-up in the Cordova article is 50% at 6 and 12 months for FVC, FEV1, RV and TLC Follow-up for 6MWD at 6 and 12 months is 46%

Note: Complication codes as follows:

PAL - Prolonged or persistent air leak
PI - Prolonged ileus
OM- Operative mortality
MI- Myocardial infarction
TP- Tension pneumothorax
CI- Cardiopulmonary instability
Inf - Infections
POM - Post-operative mortality
IS - Ischemic stroke
PE - Pulmonary embolism
THM- Total hospital mortality
GI- Gastrointestinal
PVS- Prolonged ventilator support
DP- Diaphragmatic paralysis

Note: Outcomes codes as follows:

FEV1 - Forced expiratory volume in 1 second
FVC - Forced vital capacity
PO2 - Oxygen tension
MDS- Mahler Dyspnea Scale
RV - Residual volume
6MWT - 6 minute walk test

12 MWT - 12 Minute walk test
TLC - Total lung capacity
IVC - Inspiratory vital capacity
M VV - Maximum voluntary ventilation
Borg Scale - Borg Dyspnea Index
PaCO2 - Arterial carbon dioxide tension
FS - Fletcher's Dyspnea Scale
VC - Vital capacity
Dco - Diffusing capacity
PSTAT - Static lung elastic recoil pressure
FRC - Functional residual capacity
TDI - Transition Dyspnea Index
MRC - Medical Research Council Dyspnea Scale
SGaw - Airway conductance
DLCO - Diffusing capacity for carbon monoxide
MCC - Medical center charges
PF - Professional fees
SR - Sponsor reimbursement

Table 2. Key Outcomes Reported

Study	Outcomes Recorded				
Naunheim, et al.	Month	FEV1(L)	FVC (L)	O2tension (mm Hg)	
	Pre-op	.71+/-.31	2.24+/-.94	59+/-9	
	3	96+/-.53	2.58+/-.89	67+/-11	
	Month	RV (L)	6MWT (ft)	MDS	
	Pre-op	6.21+/-1.96	771+/-285	.68+/-.7	
	3	4.13+/-1.27	923+/-343	1.1+/-.7	
Criner, et al.	Case 1	Pre-op	Post-op		
	FVC (L)	1.04	2.89		
	FEV1 (L)	.41	1.16		
	Case 2	Pre-op	Post-op		
	FVC (L)	1.08	1.80		
	FEV1 (L)	.41	.65		
	Case 3	Pre-op	Post-op		
	FVC (L)	1.15	2.04		
	FEV1 (L)	------	.56		
Bingisser, et al.	Months	FEV1 (L)	RV (L)	12MWT (m)	
	Pre-op	.82 +/- 25	5.6 +/-1.3	35-790	
	3 Post-op	1.09 +/- 31*	4 3 +/- 9**	175-1035	
	Months	FVC (L)	TLC (L)	IVC (L)	RV/TLC(%)
	Pre-op	2.54+/- 8	8 78+/-1.43	3.03+/-1.02	64+/-.09
	3 Post-op	3 27+/- 62*	7.34+/-1.23***	3.51+/- 86***	.55+/-.07**
	* p<0 01 compared with preoperative value.				
	** p<0.05 compared with preoperative value.				
	*** p<0.001 compared with preoperative value.				
Gaissert, et al.	Months	FEV1 (L)	6MWT (ft)	Po2 (mmHg)	MDS
	Pre-op	.72	1131	62	3.2
	3 Post-op	1.19	1345	69	---
	6 Post-op	1 29	1449	74	---
	These results reflect the mean for the total volume reduction group. Graphs were provided for results at 12 months post-op but the charts only showed results to 6 months out				

Study	Outcomes Recorded
Zenati, et al.	Month FEV1 (L) FVC (L) RV (L) MVV (L/min) Pre-op .64+/-.22 2.12+/-.68 5.62+/-1.67 28.1+/-9.7 3 Post-op .97+/-.38 2.76+/-.79 4.26+/-1.2 38.5+/-12.8 Month 6MWT (ft) Dyig PCO2 (mmHg) TLC (L) Pre-op 504+/-282 3.7+/-1.8 44.9+/-6.5 7.8+/-1.8 3 Post-op 1012+/-229 2.4+/-1.2 41.6+/-5 7.2+/-1.5
Roue, et al.	Month FEV1 (mL) TLC (mL) PaO2(mmHg) PaCO2 FS Pre 420-880 4640-9980 43-65 40-55 4-5 6 310-1200 4220-8340 45-73 31-50 1-5 12 440-1180 --- 47-79 30-44 1-5 18 630-1430 --- 30-78 31-47 1-5 24 540-1170 --- 37-57 35-50 2-5 36 580-1170 --- 53-62 33-56 2-5 48 600-820 --- 51-59 37-39 4-5 For FEV1, 13 of 13 were followed to 6 months; 9 of 13 to12 months; 7 of 13 to 18 months; 6 of 13 to 24 months; 5 of 13 to 36 months; and 3 of 13 to 48 months. For TLC, 7 of 13 were followed to 6 months. For PaO2/PaCO2, 13 of 13 were followed to 6 months; 8 of 13 to 12 months; 6 of 13 to 18 months; 6 of 13 to 24 months; 3 of 13 to 36 months, and 2 of 13 to 48 months. For FS, 13 of 13 were followed to 6 and 12 months; 12 of 13 to 18 months, 10 of 13 to 24 months; 6 of 13 to 36 months; 3 of 13 to 48 months
Kotloff, et al	MS Group Month FEV1 (L) FVC (L) RV (L) 6MWT (ft) Pre-op .73+/-.24 2.28+/-.72 4.95+/-1.06 999+/-241 3-6 Months 1.02+/-.4 2.65+/-.78 3.49+/-.88 1181+/-287 VATS Group Month FEV1 (L) FVC (L) RV (L) 6MWT (ft) Pre-op .73+/-.24 2.13+/-.71 4.89+/-1.07 969+/-305 3-6 Months 1.0+/-.37 2.72+/-.89 3.79+/-.89 1244+/-331

Study	Outcomes Recorded
Gelb, et al.	Month / FEV1(L) / FVC (L) / RV (L) / VC (L) Pre-op / .71+/- 06 / 2.3+/-.2 / 6.8+/-.3 / 2.8+/-.2 6 / 1.19+/-.1 / 3.1+/-.2 / 4.9+/-.3 / 3.2+/-.7 12 / .95+/-.1 / 2.6+/-.2 / 5.5+/-.3 / 2.9+/-.2 Month / Dco (mmHg) / PSTAT (cm H2O) / TLC (L) Pre-op / 5.0+/-1.0 / 1.3+/-.2 / 9.5+/-.3 6 / 8.6+/-.70 / 2.8+/-.2 / 8.0+/-.3 12 / 10.0+/-1.0 / 3.0+/-.2 / 8.5+/-.3 These statistics show no distinction between the patients who received the bilateral thoracoscopic stapling technique and the sequential bilateral VATS procedure.
O'Donnell, et al.	Month / FEV1 (L) / FVC (L) / TLC (L) / RV (L) Pre-op / 1.13+/-.08 / 2.63+/-.27 / 8.02+/-.40 / 5.28+/-.31 Post-op / 1.44+/-.12 / 3.09+/-.21 / 6.91+/-.33 / 3.73+/-.33 Month / FRC (L) / Borg Pre-op / 6.17+/-.39 / 3.1+/-.4 Post-op / 5.03+/-.32 / 5.8+/-.8 TDI and MRC improved by 112+/-47% and 38+/-14%, respectively. The article does not specify at what time interval the post-op results were gathered
Miller, et al.	Month / FEV1 (L) % predicted / FEV1/FVC % predicted / FVC (L) % predicted / MVV % predicted Pre-op / 0.56 / 24% / 57% / 18% 1 / 0.65 / 39% / 64% / 24% 3 / 1.08 / 49% / 80% / 31% 6 / 1.10 / 52% / 85% / 40% Month / PO2 (mmHg) / PCO2 (mmHg) / 6MWT (ft) Pre-op / 62 / 43 / 785 1 / 65 / 41 / 1020 3 / 72 / 38 / 1250 6 / 70 / 40 / 1600

Study	Outcomes Recorded
Argenziano, et al.	Month / FEV1 (mL) / FVC (mL) / 6MWT (ft) / MRC Pre-op: 579+/-361 / 1668+/-907 / 703+/-211 / 5.28+/-.31 Post-op: 841+/-431 / 2239+/-684 / 1012+/-334 / 3.73+/-.33 Post-op results represent data collected between 3 and 6 months after surgery for patients with concomitant tumors. Although the text states that followup was done at 3, 6 and 12 months, there is no chart summarizing the follow-up of the general population of patients undergoing LVRS for this study. However, the text states "preoperative characteristics as well as postoperative results were not significantly different from these of the total patient population."
Eugene, et al.	Month / FEV1 (L) / FVC (L) / RV / TLC Pre-op: .41+/-.01 / 1.31+/-.06 / 301%+/-9.2% / 141%+/-3.1% 1: .57+/-.02 / 1.7+/-0.1 / 211%+/-5.2% / 108%+/-5.4% 3: .63+/-.04 / 1.83+/-.13 / ----- / ----- 6: .62+/-.03 / 1.96+/-.15 / ----- / ----- 12: .62+/-.05 / 2.05+/-.12 / ----- / ----- Month / Borg / MRC Pre-op: 7.6 / 3.9 1: ---- / ---- 3: ---- / ---- 6: 4.65 / 2.35 12: ---- / ----
Gelb, et al.	Month / FEV1 (L) / FVC (L) / RV (L) / TLC (L) Pre-op: .69+/-.10 / 2.48+/-.14 / 6.72+/-.30 / 9.31+/-.33 Post-op: 1.16+/-.16 / 2.93+/-.21 / 4.7+/-.31 / 7.67+/-.39 Month / FRC (L) / SGaw (LPS/cm H2O/L) / DLCO (mm/Hg) Pre-op: 7.26+/-.30 / .02+/-.003 / 2.7+/-.6 Post-op: 5.57+/-.33 / .04+/-.003 / 8.0+/-.6 The post-op results were taken at five to six months after LVRS.

Study	Outcomes Recorded

McKenna

Patient	Pre-op FEV1 (L) % predicted	Post-op FEV1 (L) % predicted
1	.66	.69
2	.77	.76
3	.64	1.12
4	.95	.97
5	.68	1.12
6	.56	.84
7	.89	1.31
8	.48	1.4
9	.72	2.12
10	.33	-----
11	.53	.63

This article does not specify at what time interval the post-op results were gathered.

At the time of publication, all patients except for #9 were alive. Four patients had the same pulmonary function after the surgery, one was improved and six were much improved.

At the time of publication, three patients were 22 months out, one was 16 months out, one was 12 months out, three were seven months out, one was three months out and one was two months out. Patient #9 died at 10 months out.

Yusen, et al.

Month	FEV1 (L)	FVC (L)	RV (L)	TLC (L)
Pre-op	69+/-.27	2.48+/-.75	5.9+/-1.26	8.34+/-1.48
3	1.09+/-.49	2.78+/-.79	3.95+/-1.06	6.76+/-1.23
6	1.13+/-.60	2.95+/-.85	3.92+/-.98	6.93+/-1.16
12	1.29+/-.51	3.16+/-.77	4.16+/-.94	7.39+/-1.51

Month	PaO2 (mm Hg)	6MWT(ft)	MRC	MDS
Pre-op	60+/-10	1122+/-336	2.5	.86
3	68+/=12	1288+/-331	1.33	1.68
6	70+/-12	1403+/-274	.88	2.5
12	73+/-10	1478+/-261	.64	2.4

Study	Outcomes Recorded
Cooper, et al.	Month FEV1 (L) FVC (L) RV (L) TLC (L) Pre-op .70 (.69) 2.5 (2.4) 6.0 (5.7) 8.4 (8.1) 6 1.06 (1.1) 3.0 (3.0) 4.3 (4.1) 7.2 (7.1) 12 (1.0) (3.0) (4.3) (7.3) Month PaCO2 (mmHg) 6MWT (ft) PaO2 (mmHg) Pre-op 43 (43) 1125 (1150) 62 (63) 6 39 (38) 1311 (1362) 70 (72) 12 (37) (1357) (71) Month MRC MDS Pre-op 2.8 (NA) 8? (NA) 6 1.2 (NA) 2.2 (NA) 12 (NA) (NA) The values recorded that do not appear in parenthesis reflect follow-up of 101 patients at six months post-LVRS. The values recorded that appear in parenthesis reflect follow-up of 56 patients at six months and one year post-LVRS.
Sciurba, et al.	Month 6MWT(ft) TLC(L) RV(L) FRC(L) Pre-op 819+/-284 7.84+/-1.68 4.85+/- 1.06 5.98+/-1.16 Post-op 916+/-286 7.36+/-1.78 4.08+/-.94 5.22+/-1.3 Month FEV1(L) FVC(L) PaCO2(mmHg) DCO(mmHg) Pre-op .87+/- 36 2.77+/-1.16 42+/-6 8.7+/-4.7 Post-op 1.11+/- 45 3.14+/-1.15 38+/-5 9.6+/-3.5 Month TDI Pre-op ---- Post-op 5.1+/-1.8 The chart does not specify at what time interval the post-op results were gathered, however the graphs included in the article plot results at 3 months post-op.

Study	Outcomes Recorded				
Cordova, et al.	Month	FVC(L)	FEV1(L)	TLC(L)	RV(L)
	Pre-op	2.39+/-.70	.68+/-.19	7.2+/-1.87	4.77+/-1.5
	3	2.91+/-.63	.93+/-.29	6.4+/-1.36	3.47+/-1.2
	Month	FRC(L)	MVV(L/min)	PaCO2(mmHg)	6MWT(m)
	Pre-op	5.9+/-1.53	28+/-9.6	45+/-6	251+/-114
	3	4.42+/-1.3	38+/-14	43+/-6	340+/-84

Study	Outcomes Recorded
Brenner, et al.	This article compared various LVR surgical procedures. The greatest improvement in FEV1 and overall patient function appear to occur with the bilateral stapling procedures independent of the surgical approach (VATS vs. sternotomy). The morbidity and mortality for patients who underwent a unilateral VATS procedure for either staple LVR or contact tip Nd:YAG were essentially the same except for an 18% incidence of delayed pneumothorax following the laser procedure. Patients who underwent staple procedure had greater improvement in oxygen independence in 6-month follow-up FEV1 (33% vs. 13%) and in overall lifestyle and dyspnea scale when compared with patients treated with Nd:YAG contact laser. Overall, the results showed greater improvement in dyspnea, oxygen independence, prednisone independence and pulmonary function for the bilateral procedure compared with the unilateral procedure. Available data suggest that standard operation at this time for a patient with severe heterogeneous emphysema should be bilateral staple lung volume reduction procedures performed by either median sternotomy or VATS. All patients had improvement in the transitional dyspnea index and the 16 patients with improved lung elastic recoil had significantly greater improvement in 6-minute walk distance than the four patients whose conditions did not improve. Despite the recent documentation in short-term improvement following LVRS, it is uncertain whether long-term improvements will be realized. Centers of excellence should be established where LVRS may be performed. A national registry should be initiated to collect multi center data to commence answering the scientific questions.

Study	Outcomes Recorded
Albert, et al.	Median hospital stay was 8.0 days; there were no deaths. The median charge was $26,669 of which 73% was for medical center services and 27% was for physician services. Fees for medical center rooms and operating suite time accounted for 71% of medical center charges. Charges by surgeons and anesthesiologists accounted for 77% of professional fees. Total charges were related directly to length of stay. Median reimbursement for medical center services was $22,264, resulting in a median total reimbursement that represented 94% of total charges. The median reimbursement-to-cost ration was 1.22, compared with 1.05 for all medical services in fiscal year 1995. In theory, the expense of LVRS, which this article estimated at approximately $4.6 billion, would be offset if the procedure extended life, improved quality of life and/or reduced the amount of money spent on outpatient clinic visits, hospitalizations, medications and/or oxygen therapy. Whether this is indeed the case remains to be determined.
Slone, et al.	The primary candidates for LVRS are individuals with severe debilitating emphysema despite optimal medical management. The most common reason for exclusion is an unsatisfactory distribution and severity of emphysema based on imaging studies. Target areas of the lung are selected based on preoperative imaging studies and intraoperative observation, including the delayed collapse of severely emphysematous lung compared with rapid absorptive atelectasis observed in the more normal lung when the airway is occluded. Although a number of procedures and variations have been practiced and advocated, including a unilateral procedure in select patients, the bilateral procedure has demonstrated the greatest overall benefit.
Tonelli, et al.	Therapies should be considered experimental whenever the evidence regarding effectiveness and risk is insufficient to provide patients considering the procedure with the type of information that satisfies the usual practice standards of informed consent.

Study	Outcomes Recorded

Naunheim, et al.

PREOPERATIVE PROFILE

First Author	Modality	# Patients	FEV1 % predicted	RV % predicted	6MWT (ft)	O2 Use
Wakabayashi	CO2 laser	22	.73	-----	-----	59%
Little	Nd:YAG	55	.74	-----	-----	73%
Hazelrigg	Nd:YAG	141	.63	5.52	646	79%
McKenna	Nd:YAG	33	.70	5.10	-----	75%
Eugene	Both	28	.68	5.07	-----	82%
Wakabayashi	Both	443	-----	-----	-----	70%
Keenan	Resection	57	.82	5.10	754	80%
McKenna	Resection	39	.70	5.40	-----	69%
Naunheim	Resection	50	.73	5.13	864	74%
McKennan	Resection	79	.69	4.80	----	56%
Bingisser	Resection	20	.80	5.80	1608 (12min)	35%
Cooper	Resection	100	.70	5.90	1175	90%
Miller	Resection	100	.60	5.50	1106	71%
Daniel	Resection	26	.73	6.10	-----	54%
Miller	Resection	53	.56	-----	785	89%
Argenziano	Resection	85	.55	4.0	589	69%

Study	Outcomes Recorded

Naunheim, et al (cont.)

POSTOPERATIVE PROFILE

First Author	Modality	FEV1*	RV**	6MWT*	O2 Use	Mortality
Wakabayashi	Uni-VATS	30	-----	-----	-----	18.0%
Little	Uni-VATS	15	-----	-----	-----	5.5%
Hazelrigg	Uni-VATS	14	11	-----	65%	5.7%
McKenna	Uni-VATS	13	-----	-----	36%	0
Eugene	Uni-VATS	34	12	-----	64%	0
Wakabayashi	Uni-VATS	26	12	-----	-----	5.6%
Keenan	Uni-VATS	27	16	14	63%	5.3%
McKenna	Uni-VATS	33	-----	-----	13%	2.5%
Naunheim	Uni-VATS	35	33	20	40%	4.0%
McKenna	Bi-VATS	52	-----	-----	18%	1.0%
Bingisser	Bi-VATS	37	24	39	30%	0
Cooper	Bi-Open	57	32	19	27%	5.0%
Miller	Bi-Open	83	29	29	18%	10.0%
Daniel	Bi-Open	40	30	-----	41%	3.8%
Miller	Both-Open	97	-----	104	18%	5.2%
Argenziano	Both-Open	61	-----	62	-----	7.1%

* Percent increase
** Percent decrease

TABLE 7
UNANSWERED QUESTIONS ABOUT THE RISKS AND BENEFITS
OF LVRS AND STUDY DESIGN ISSUES

IMPORTANT UNANSWERED QUESTIONS	PRINCIPAL WEAKNESSES IN DESIGN OF CURRENT STUDIES AND CORRESPONDING DATA
Impact on health related quality of life	1, 2, 4
Impact on morbidity/mortality profiles	1, 2, 3
Durability of any benefits to LVRS	2, 3
Appropriate patient selection criteria	3, 5
Relationships between surrogate and final (patient) outcomes	1, 4
Role of pulmonary rehabilitation in outcomes	1, 5

KEY

1 = study design issues, lack of control group or natural history

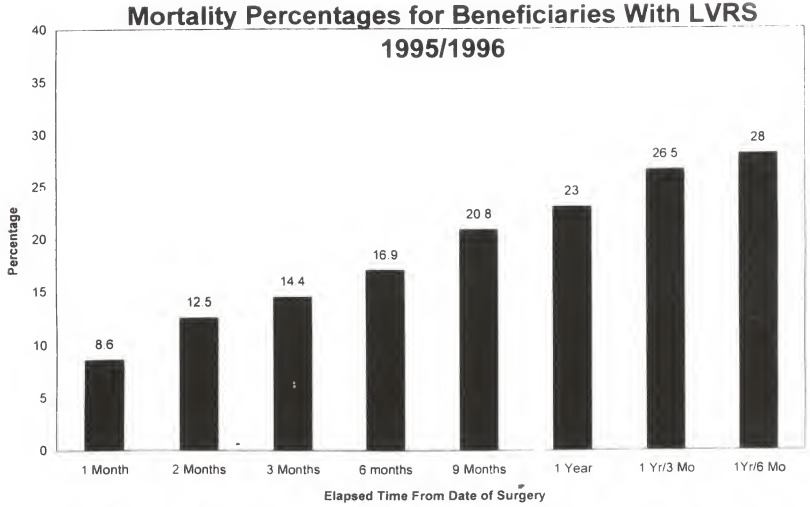
2 = brevity of follow-up period

3 = inconsistent and incomplete follow-up

4 = important outcomes not measured

5 = criteria for patient selection to surgery and variable across studies and/or reporting of inclusion criteria uncertain

Chart 1


Mortality Percentages for Beneficiaries With LVRS
1995/1996
Percentage
40
35
30
25
20
15
10
5
0
8.6
12.5
14.4
16.9
20.8
23
26.5
28
1 Month
2 Months
3 Months
6 months
9 Months
1 Year
1 Yr/3 Mo
1Yr/6 Mo
Elapsed Time From Date of Surgery

APPENDIX

National Emphysema Treatment Trial

Clinical Centers	Principal Investigator	Co-Principal Investigator
Baylor College of Medicine 6565 Fannin, A886 Houston, Texas 77030 Patient Referral: Charles Miller, Ph.D. 1-(800)-622-9567	Rafael Espada, M.D.	Joseph Rodarte, M.D.
Brigham & Women's Hospital Division of Pulmonary Medicine Tower 4B 75 Francis Street Boston, Massachusetts 02115 Patient Referral: Tammy Weihrauch 1-(888)-294-5864	John Reilly, M.D.	David Sugarbaker, M.D.
Cedars-Sinai Medical Center 8635 West Third Street Suite 975 W Los Angeles, California 90048 Patient Referral: Brenda Williams 1-(800)-CEDARS-1	Robert McKenna, M.D.	Zab Mohsenifar, M.D.
Cleveland Clinic Foundation 9500 Euclid Avenue Cleveland, Ohio 44195 Patient Referral: Barbara Higgins 1-(800)-223-2273, Ext. 54215	Janet Maurer, M.D.	Atul Mehta, M.D.
Columbia University 161 Fort Washington Avenue Room 310 New York, New York 10032 Patient Referral: Patricia Jellen (212) 305-1158	Mark Ginsburg, M.D	Steven Scharf, M.D., Ph.D
Duke University Box 3864 Durham, North Carolina 27710 Patient Referral: Janet Johns (919) 681-2720	Neil MacIntyre, M.D.	R. Duane Davis, M.D.

Mayo Foundation 200 1st Street Southwest Rochester, Minnesota 55905 Patient Referral: Kristin Bradt (507) 284-4619	Rolf Hubmayr, M.D.	Claude Deschamps, M.D.
National Jewish Medical Center 1400 Jackson Street Denver, Colorado 80206 Patient Referral: Lung Line 1-(800)-222-LUNG	Reuben Cherniack, M.D.	Barry Make, M.D.
Ohio State University North 325 Means Hall 1654 Upham Drive Columbus, Ohio 43210 Patient Referral: Mary Lou Coffee (614) 293-4509	Philip Diaz, M.D.	Patrick Ross, M.D.
St. Louis University 3635 Vista Avenue St. Louis, Missouri 63110 Patient Referral: Gina Roelke 1-(800)-268-5880	Keith Naunheim, M.D.	Cesar Keller, M.D.
Temple University 3401 North Broad Street Suite 931 Parkinson Pavilion Philadelphia, Pennsylvania 19140 Patient Referral: Anne Marie Kuzma (215) 707-1334	Gerard Criner, M.D.	Satoshi Furukawa, M.D.
University of California-San Diego 200 West Arbor Drive San Diego, California 92103 Patient Referral: Trina Limberg (619) 294-6066	Andrew Ries, M.D., M.P.H.	Robert Kaplan, Ph.D.
University of Maryland 22 South Greene Street Baltimore, Maryland 21201 Patient Referral: Karen King (410) 328-2168	Mark Krasna, M.D.	Jonathon Orens, M.D.

University of Michigan 1500 East Medical Center Drive Ann Arbor, Michigan 48109 Patient Referral: Telecare 1-(800)-742-2300	Fernando Martinez, M.D.	Mark Iannettoni, M.D.
University of Pennsylvania 3400 Spruce Street Philadelphia, Pennsylvania 19104 Patient Referral: Penn Health Customer Service 1-(800)-789-PENN	Larry Kaiser, M.D.	John Hansen-Flaschen, M.D.
University of Pittsburgh 200 Lothrop Street Suite C-700 Pittsburgh, Pennsylvania 15213 Patient Referral: Betsy George (410) 648-6736	Robert Keenan, M.D.	Frank Sciurba, M.D.
University of Washington BB-1253 Health Sciences Building Box 356522 Seattle, Washington 98195 Patient Referral: Doctors, Inc. 1-(800)-826-1121	Joshua Benditt, M.D.	Douglas Wood, M.D.
Washington University Suite 3908 Queeny Tower One Barnes Hospital Plaza St. Louis, Missouri 63110 Patient Referral: Deen Scharff (314) 362-6044	Joel Cooper, M.D.	Stephen Lefrak, M.D.

Resource Centers

Johns Hopkins, NETT Coordinating Center
615 North Wolfe Street
Room 5010
Baltimore, Maryland 21205
Steven Piantadosi, M.D., Ph.D., Center Director
James Tonascia, Ph.D., Co-Investigator
(410) 955-8175

National Heart, Lung and Blood Institute
31 Center Drive-2486
Building 31, Room 5A52
9000 Rockville Pike
Bethesda, Maryland 20892
Gail Weinmann, M.D., Project Officer
Joanne Deshler, M.S., Contracting Officer
(301) 435-0340

Health Care Financing Administration
7500 Security Boulevard
Baltimore, Maryland 21244
Steven Sheingold, Ph.D., Director, Division of Program Analysis and Performance Measurement
Karen McVearry, Health Insurance Specialist
(410) 786-4643

Agency for Health Care Policy and Research
Kaiser Permanente Building
2102 East Jefferson Street, Suite 600
Rockville, Maryland 20852
Carolyn Clancy, M.D., Director, Center for Outcomes and Effectiveness Research
(301) 594-1357, Ext. 1338

Executive Committee

Alfred Fishman, M.D., Chairman
University of Pennsylvania Health System
3400 Spruce Street, Gates Building, 5th Floor
Philadelphia, Pennsylvania 19104

Steven Piantadosi, M.D., Ph.D., Vice-Chairman
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Stephen Lefrak, M.D.
Neil MacIntyre, M.D.
Barry Make, M.D.
Fernando Martinez, M.D.
Janet Maurer, M.D.
Rob McKenna, M.D.
Zab Mohsenifar, M.D.
Keith Naunheim, M.D.
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Patrick Ross, M.D.
Steven Scharf, M.D., Ph.D.
Frank Sciurba, M.D.
David Sugarbaker, M.D.
James Tonascia, Ph.D.
Gail Weinmann, M.D.
Douglas Wood, M.D.

Chairmen, Phase I Protocol Workgroups

Andrew Ries, M.D., Maximal Medical Therapy Subcommittee
Reuben Cherniack, M.D., Patient Assessment Subcommittee
Steven Piantadosi, M.D., Ph.D., Statistical Design and Methods Subcommittee
Larry Kaiser, M.D., Surgical Procedures Subcommittee

OP/STAFF DIV: HCFA Date:

Summary Statement

Subject: Report to Congress Concerning Medicare Coverage of Lung Volume Reduction Surgery

Purpose

This report is required by section 212 of the 1997 Appropriations Act (P.L. No. 104-208, 110 Stat. 3009, 1997). This section requires the Administrator of HCFA, with the advice and technical assistance of AHCPR, to review all available studies and research data on lung volume reduction surgery (LVRS) as a treatment for end-stage emphysema and chronic obstructive pulmonary disease. In addition, this report is to include a recommendation regarding the appropriateness of Medicare coverage for such procedures.

Summary

Currently, Medicare covers LVRS only when provided under the protocol of the National Emphysema Treatment Trial (NETT). The NETT is a cooperative effort between HCFA and the National Heart, Lung and Blood Institute implemented in April 1996. The agreement followed a technology assessment by AHCPR which stated that scientific conclusions regarding the risks and benefits of LVRS could not be drawn from current data. AHCPR recommended that HCFA consider covering the procedure within a controlled, clinical study.

For this report, HCFA reviewed 26 articles that were published subsequent to the AHCPR technology assessment. We also analyzed relevant Medicare claims data to provide supporting information. The conclusion from these analyses is that current data cannot provide answers to the most significant questions concerning the risks and benefits of LVRS for Medicare beneficiaries. Therefore, HCFA's current coverage policy, which provides controlled access to LVRS under conditions that will provide the needed data to guide future coverage decisions, remains the appropriate course.

Concerns

None

Recommendations/Conclusions

Transmit this report to the President of the Senate, Speaker of the House, and Chairmen of the Senate Finance Committee, the House Ways and Means Committee, and the House Energy and Commerce Committee.

Contact Person: Karen McVearry, HCFA/OCSQ/CAG, 410-786-4643

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